American Journal of Obstetrics and Gynecology

VOL. 46 AUGUST, 1943 No. 2

Original Communications

EXCRETION OF ESTROGEN AND GONADOTROPIN IN LATE PREGNANCY*†

With Especial Reference to the Toxemias of Pregnancy and to Quantitative Methods

RUTH M. WATTS, PH.D., AND FRED L. ADAIR, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-in Hospital)

THE etiology of the toxemias of pregnancy, especially pre-eclampsia and eclampsia, has remained obscure. Among the recent theories to be advanced have been those concerning the role of sex hormones. From extensive and detailed studies Smith and Smith[1-13] have concluded that the excretion of estrogen is low and that of gonadotropin high in pre-eclampsia and eclampsia and that "The close correlation between the clinical and hormonal findings and the fact that both abnormalities may be alleviated by estrogen and progestin administration (even though only temporarily in the severe pre-eclamptics) has led us to the conclusion that the clinical manifestations of pre-eclampsia are the direct result of a changed metabolism of sex steroids involving a greatly increased rate of destruction and accountable to estrogen and progestin deficiency."[13] On the other hand Taylor and Scadron[15] (1939) have concluded concerning the estrogens and gonadotropins that "the significance of these hormone differences between normal and toxemic patients is still a matter of theory," "that there was evidence of a frequent but not invariable lowering of the estrogen values in the toxemic cases and of an

*This work has been done under a grant from the Douglas Smith Foundation for Medical Research of The University of Chicago.

†Read, in part, at a meeting of the Chicago Gynecological Society, February 19, 1943.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

elevation of prolan values in a few cases only," and that "the hormone changes observed in the toxemic patients are perhaps associated with the cause of toxemia but may simply be the result of disturbed kidney, liver or placental physiology." In general, our preliminary note[14] and the reports of other workers corroborate the findings of low estrogen and high gonadotropin values. Reviews of the subject have been published by others.[15]

This investigation was undertaken in 1934 shortly after the first reports of Smith and Smith.[1, 2] The purpose was to further the study of the relationship of hormones (estrogens and gonadotropins) to the toxemias of late pregnancy (1) by a rigid clinical classification of the material, (2) by pharmacologic assay of the hormones, and (3) by a statistical interpretation of the laboratory findings. At the time this work was begun pharmacologic assay on blood was impossible for toxemic patients because of the large amount of blood required for such an assay. Therefore, the problem was undertaken from the standpoint of the excretions of estrogens and gonadotropins. We realize the limitation of such an approach to the problem without the study of blood values and also the desirability of fractionation of the estrogens.

The classification used was that of the American Committee on Maternal Welfare:[16]

Group A. Disease not peculiar to pregnancy
- I. Hypertensive disease
- II. Renal disease

Group B. Disease dependent on or peculiar to pregnancy
- I. Pre-eclampsia
- II. Eclampsia

Because of the small number of cases Group A representing coexisting conditions was not subdivided in this study. Particular emphasis has been placed on the final diagnosis after postpartum observation in all cases.

Since, in 1935, quantitative methods of extraction of both estrogens and gonadotropins and their quantitative assay were in early stages of investigation considerable attention was given to the development of these procedures and the methods then adopted have been used throughout this study (1935-1940). Since the graded dose procedure commonly used for "quantitative" assay results in great discrepancy due to failure to split dosages with less than a 50 to 100 per cent or more variation, standard dose-effect curves were prepared for both substances. This obviated difficulties in splitting dosages and minimized the error due to biologic variations observed when small numbers of animals are used for biologic assays. Methods of extractions of both estrogens and gonadotropins were studied.

Even with pharmacologic assays variations in the amounts of hormone excreted are great not only between different patients but also between

different specimens of the same patient. There is also extreme overlapping of the individual values in the different classifications of patients. Thus it becomes very difficult unless a value is extreme to allocate it to a certain clinical group (Figs. 3 and 4). With such data averages often give erroneous and distorted results. Consequently, we have subjected our data to statistical analysis to test whether or not the differences observed in the mean values of the excretions of these hormones by the various groups are significant.

Casual inspection of our data suggested that there might be a relation between the amounts of estrogen and gonadotropin excreted by each patient, that is, a patient excreting a large amount of estrogen also tended to excrete a large amount of gonadotropin. To test this we have calculated the estrogen to gonadotropin ratio which is an arbitrary value dependent upon the units we have used but which seems to be a better index of hormone balance in individual cases than the twenty-four-hour excretion value of either estrogen or gonadotropin (Figs. 3 and 4).

In the course of the investigation the hormone excretions in other pathologic conditions of pregnancy have been studied.

Part I. Experimental Methods

1. Extraction of Estrogens and Gonadotropins From Pregnancy Urine

Estrogens.—After testing various procedures for the extraction and assay of estrogens from pregnancy urine, a method employing oil extracts was adopted. This method seemed advisable because of the well-known advantages of the administration of estrogens in oil and because the low excretion of estrogens by toxemic patients made concentration desirable. Various methods of hydrolysis of the urine were studied, in which both the acid concentration and period of hydrolysis were altered. The completeness of the extraction was also tested. Prolonged heating was employed to destroy androgens as well as to aid hydrolysis of conjugated estrogens. The estrogen was extracted with benzene for ten hours in a continuous extractor of the type designed by Gallagher, Koch and Dorfman,[17, 18] and holding a 200 to 300 c.c. specimen. A calculated amount of olive oil was added to the benzene extract and the benzene removed in vacuo. We realize the advantages of the separation of various estrogens, but in order to keep the methods uniform throughout the study and to prevent loss of activity, no attempt was made to fractionate the estrogens or purify the extracts.

Gonadotropins.—In order to preserve the gonadotropins in the pregnancy urine until a pharmacologic assay could be made, the following method was adopted for use in this study:

A portion of the twenty-four-hour refrigerated specimen of pregnancy urine was acidified with concentrated HCl to pH 5.5 (nitrazine). Ten samples of 2 to 5 c.c. each were put into conical centrifuge tubes containing 5 volumes of 95 per cent ethyl alcohol (Zondek alcohol precipitation method). These tubes were stoppered and placed in the refrigerator overnight. They were centrifugated and the supernatant fluid discarded. The precipitate containing the gonadotropin was triturated with 95 per cent ethyl alcohol without removal from the tube, centrifugated and the

washing discarded. This procedure was repeated with anhydrous ether. The dry precipitate was stored in the tube in the refrigerator. When needed, individual preparations were triturated with the desired amount of water, centrifugated and the supernatant solution used for assay.

The reliability of this method of extraction is illustrated by a comparative assay of the extract and diluted urine. Two groups of 25 paired litter mate male rats (twenty-one days old) were used. In one group all the rats received a total dose of 0.03 c.c. pregnancy urine and in the other the extract equivalent to the same amount of urine. Both groups were injected 3 times daily for three days and autopsied at ninety-six hours. In the first group on urine, 45.5 per cent gave a positive response and 54.5 per cent gave a positive response on the extract. According to the assay method described below, this gives values of 31.7 and 35.3 R.U. per c.c., respectively, or an agreement of 90 per cent by the two methods. Additional assays using extracts gave values of 34.8 and 33.3 R.U. per c.c. These data were confirmed by other similar tests.

2. Assay of Estrogens and Gonadotropins

Estrogens.—The estrogens were assayed according to the dose-effect curve method proposed by Coward and Burn,[19] D'Amour and Gustavson,[20, 21] and other workers. This consists of preparing a curve from the percentage response on varying doses of estrogen and converting it into a dose-effect curve in which the amount of estrogen giving a 50 per cent response is considered as 1 R.U. Such a curve was established for our colony using 53 ovariectomized adult Wistar rats. All injections were made in olive oil. Later another curve was prepared using crystalline estrone standardized against International Standard Estrone.* The two curves were essentially the same and agreed well with those of other workers. However, the value of the rat unit differed as anticipated; 1 R.U. was equal to 29 I.U. of estrone which agrees in magnitude with Hain and Robson[22] (33 I.U.), with Taylor and Scadron[15] (35 I.U.) but not with Smith and Smith[9] (5 I.U.), Burn and Elphick[23] (10 I.U.), or D'Amour and Gustavson[21] (13 I.U.). Because the curves were to be used for routine assay purposes the general procedure in preparation was designed to meet a routine method and differed somewhat from those previously described by others:

Ovariectomized adult Wistar rats were used for the assay. Vaginal smears were made for two weeks prior to operation and any rats showing abnormal cycles were discarded. Ten days following the operation the rats were smeared for five days and then given an "excess dose" of estrogen (a dose high enough to give full cornification in 100 per cent of the rats). No selection was made for sensitivity of the rats to estrogen. Injections were made subcutaneously; all extracts were made in olive oil. The smears were read at forty-eight hours. A positive response was taken as a smear with a predominance of cornified epithelial cells. After a positive response the rat was not injected for two weeks. After a negative response the rat was used the following week. If negative again it was given an "excess dose" of estrogen. Consequently, no point on the curve was determined on a single day. This procedure was used in both the preparation of the curve and the assays. The curve was prepared by approximately half of the rats being given ascending and half descending doses of estrogen. In the crystalline estrone curve there were 98 rats on each of the 20, 30, 40 I.U. dose and 20 additional on the 20 I.U. point and 4 more at the 40 I.U. point.

*This material was supplied by the Abbott Laboratories, North Chicago, Illinois.

For assay purposes 4 to 10 rats were injected with graded doses of the unknown extract to ascertain the approximate value of one rat unit and the dose falling on the portion of the curve showing maximal sensitivity. At the dose thus determined groups of five ovariectomized rats were injected on each of four (or five) different days. The number of positive responses was totaled and the amount of estrogen equivalent to this percentage response was determined from the curve; from this the twenty-four-hour value was calculated in terms of equivalents of international units of crystalline estrone. Injecting small groups of rats on four or more days rather than the total number on one day seemed to minimize the error due to biologic variation commonly observed when duplicate assays are performed on different days. In future work this variation could be minimized by parallel assay of standard estrogen, as recommended by Hoskins, Coffman, Koch and Kenyon,[24] and Burn.[25]

Gonadotropins.—At the time this investigation was started neither a standard unit nor standard chorionic gonadotropin was available. Consequently, the values reported here unfortunately appear in biologic units of an arbitrary standard chosen by us.

Considerable time was spent in comparison of various methods of assay using ovary and seminal vesicle weight response, and the blood point response in the ovary of immature rats. The response of either the ovary or the seminal vesicle is sensitive to small doses of chorionic gonadotropin only over a very small range in the region of the minimal dose. Furthermore, the weight response of the seminal vesicle depends upon a general development of the organ while that of the ovary depends upon the formation of both follicles and corpora lutea and is also less sensitive. In fact, weights less than those of the control group are often obtained with minimal doses as observed also by Heller, Lauson, and Sevringhaus[26] with rat pituitary extracts and Cartland and Nelson[27] with pregnant mares' serum, by Gaensbauer and Bradbury[28] with commercial preparations and Sealey and Sondern[29] with "International Standard" gonadotropin. The blood point and corpus luteum response is often difficult to ascertain on low dosage without histologic examination, which becomes laborious for large numbers of assays.

A typical comparative experiment is shown in Fig. 1. Male and female rats strictly twenty-one days old and from 55 litters were treated with pregnancy urine at total dosage levels of 0.025, 0.05, 0.1, 0.2, 0.3, and 0.5 c.c. There were 25 males and 25 females on each point on the curve. In general from each litter used, one male and one female were placed on each of three points and one in each control group. The injections were made subcutaneously twice daily for three days and the rats sacrificed at ninety-six hours. The ovaries and seminal vesicles* were weighed on a Hartmann-Braun microtorsion balance and the blood point response in the ovaries noted. The value of a positive weight response in the ovaries and in the seminal vesicle was arbitrarily set as a value which exceeded the mean weight of these organs in the control groups by more than twice the standard deviation in these groups, a value which might be anticipated to be exceeded about one time in 44 in the untreated control group. The response of the S. V. to gonadotropin is shown by Curve A, of the ovarian weight by Curve B and of the blood point response by Curve C. At levels of 0.025, 0.05, 0.1, 0.2, 0.3, 0.5 c.c., the percentages of the positive responses of the seminal vesicles were 72, 100, 100, 100,

*In dissecting the seminal vesicle, the adherent part of the coagulating gland was included.

and 100, respectively, of the ovarian weights 8, 8, 52, 56, 64, 75 per cent, respectively, and of the blood points 0, 72, 84, 52, 64, 56 per cent, respectively.

It is noted that at a total dose of 0.1 c.c. of pregnancy urine that the blood point response was 84 per cent, the ovarian weight response 52 per cent, and the seminal vesicle response 100 per cent. At the region of minimal dose and of maximal sensitivity the blood point response and seminal vesicle weight response are parallel. The region of maximal response to changes in dosage is at a very low level. Furthermore the percentage value is influenced less by an extreme value than the mean weight of the entire group would be. From this and similar experiments the seminal vesicle response was selected for our assay purposes. The reliability of the seminal vesicle weight response for assay of chorionic

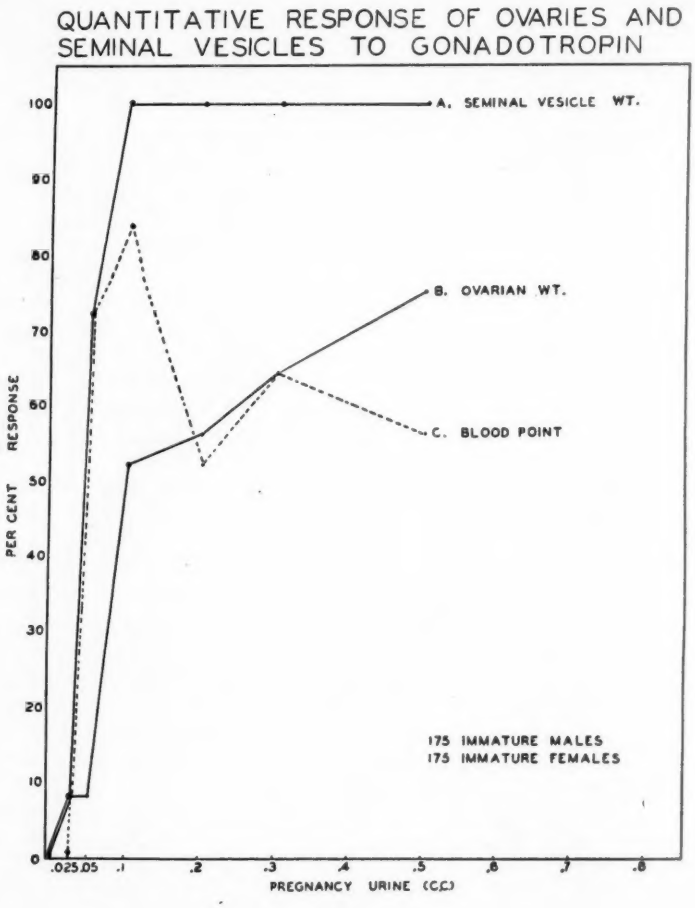

Fig. 1.

gonadotropin has been shown by Deansley,[30] Korenchevsky, Dennison, and Simpson,[31] D'Amour and D'Amour,[33] Bischoff[32] and Sealey and Sondern.[29] It also meets the requirements of the League of Nations Health Organizations[34] for comparison of the International Standard of chorionic gonadotropin.

A study was made of the effect of the variation in the spread of the injection and the results are in agreement with other workers. Two groups of 20 litter mate male rats (twenty-one days old) were injected simultaneously with extracts of pregnancy urine (0.02 c.c. total dose). Group 1 received 1 injection subcutaneously daily for three days, and Group 2 received 2 injections daily for three days. Both groups were sacrificed at ninety-six hours, and the amount of hormone determined by the assay curve. Group 1 gave 50 per cent positive responses, and Group 2, 65 per cent, corresponding, respectively, to 50 R.U. and 60 R.U. c.c. Thus in this experiment the value when only three injections were given was 16.7 per cent below that when six injections were given.

For assay purposes a dose-effect curve was constructed from a composite specimen of pregnancy urine. Rats from 47 litters of twenty-one-day-old rats were used. In general one litter mate was placed on each of two or three different dosages and one saved for a control. The positive response was taken as the weight exceeding the mean by twice the standard deviation of the control group of 30 rats. There were 20 rats at 0.025, 38 each at 0.05, 0.0625, and 0.075 c.c., 14 at 0.1 c.c., and 12 at

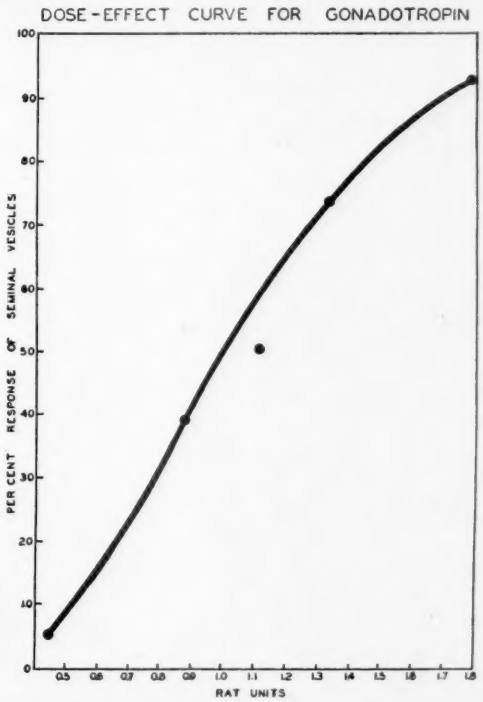

Fig. 2.

0.15 c.c. total dose of pregnancy urine; percentages of positive responses were 5, 39.5, 50.0, 73.7, 93.0, and 100, respectively. The dose giving a 50 per cent response on the curve was considered as equivalent to 1 R.U. and the dose-effect curve constructed in terms of rat units (Fig. 2).

In assaying by this method, a preliminary test was made on 4 to 10 rats in order to determine the region of the 50 per cent response. At this dose level, 15 to 25, strictly 21-day-old, male rats were injected with the same dose. This was done using rats from as many different litters as possible and injecting on different days. Litter mates from the same

litters were reserved for a control group. The percentage of responses in which the seminal vesicle weight exceeded twice the standard deviation of the mean of the control group was determined. Using the assay curve in Fig. 2, the amount of hormone in the dose tested was determined and from this the excretion per twenty-four hours calculated. The control group was compiled monthly. This obviated possible error due to seasonal variation in organ weights.

Such a method was found to be simple and to give reproducible results and offers the possibility of extrapolating dosage and minimizing the error due to biologic variation, as we have cited previously.[35] The accuracy of the method is illustrated in Table I. In 10 assays in which there were more than 10 rats in the assay group, seven of 10 agreed within 90 per cent or better. The effect of the number in the group upon the accuracy of the assay was shown by taking 14 assays, each with 20 animals in the group, and subdividing them into smaller groups and comparing the resulting values. For example, the group of 20 tests was compared with the first 15 tests, and with the first and second groups of 10 and the two groups of 10 with each other. The results are shown in Table II. If only the first 15 rats had been used in the assay, 12 of the 14 assays would have had an agreement of 90 per cent or better, 9 of 14, 95 per cent or better, and all within 85 per cent. Had either the first group or second group of 10 been used only seven of 14 would have agreed within 90 per cent. Only one of 14 of the two groups of 10 each agreed within 90 per cent. From this it was decided to assay using 15 to 25 rats for each assay.

TABLE I. QUANTITATIVE ASSAY OF GONADOTROPIN

NUMBER	TOTAL DOSE PREG. URINE (C.C.)	NO. MALES	PER CENT POSITIVE	RAT UNITS		PER CENT AGREEMENT
				PER DOSE	PER C.C.	
26-1	0.010	12	25.0	0.74	74.0	
	0.015	20	65.0	1.20	80.0	93
26-2	0.02	16	25.0	0.74	37.0	
	0.03	16	50.0	1.00	33.3	90
26-3	0.015	20	30.0	0.79	52.7	
	0.200	20	50.0	1.00	50.0	95
	0.030	20	80.0	1.45	48.3	91, 97
26-6	0.02	15	53.3	1.04	52.0	
	0.02	20	65.0	1.20	60.0	87
26-7	0.015	20	25.0	0.74	49.3	
	0.020	16	56.3	1.08	54.0	91
30-1	0.03	23	34.8	0.84	28.0	
	0.04	16	75.0	1.36	34.0	82
30-2	0.03	20	55.0	1.06	35.3	
	0.03	16	50.0	1.00	33.3	94
35-1	0.20	19	42.1	0.91	4.6	
	0.30	13	69.2	1.26	4.2	91
36-2	0.04	16	75.0	1.36	34.0	
	0.05	16	81.3	1.47	29.4	86
47-1	0.15	16	37.5	0.87	5.8	
	0.20	16	68.8	1.25	6.3	92

Part II. Excretion of Estrogens and Gonadotropins in Normal Pregnancy and in Toxemias of Pregnancy

The estrogen and gonadotropin excretion has been studied in 57 cases during late pregnancy (average 35 weeks) and a statistical study of the comparison of the excretion in normal pregnancy and toxemias has been made.

TABLE II. EFFECT OF NUMBER OF TEST ANIMALS ON ACCURACY OF QUANTITATIVE ASSAY OF GONADOTROPIN

P.U. NUMBER	TOTAL DOSE P.U. (C.C.)	NO. MALES	PER CENT POSITIVE	RAT UNITS		PER CENT AGREEMENT BETWEEN GROUPS			
				PER DOSE	PER C.C.	20:15	20:10	20:10	10:10
15-1	0.05	20	75.0	1.36	27.2	98	83	81	67
		15	73.3	1.33	26.6				
		10	60.0	1.13	22.6				
		10	90.0	1.68	33.6				
26-1	0.015	20	65.0	1.20	80.0	98	94	95	89
		15	66.7	1.22	81.3				
		10	60.0	1.13	75.3				
		10	70.0	1.27	84.6				
26-3	0.015	20	30.0	0.79	52.7	85	85	89	75
		15	20.0	0.67	44.7				
		10	20.0	0.67	44.7				
		10	40.0	0.89	59.3				
26-3	0.02	20	50.0	1.00	50.0	96	79	79	62
		15	46.7	0.96	48.0				
		10	30.0	0.79	39.5				
		10	70.0	1.27	63.5				
26-3	0.03	20	80.0	1.45	48.3	92	88	100	88
		15	73.3	1.33	44.3				
		10	70.0	1.27	42.3				
		10	80.0	1.45	48.3				
26-6	0.02	20	65.0	1.20	60.0	98	83	83	69
		15	66.7	1.22	61.0				
		10	50.0	1.00	50.0				
		10	80.0	1.45	72.5				
26-7	0.015	20	25.0	0.74	49.3	97	94	91	85
		15	26.7	0.76	50.7				
		10	30.0	0.79	52.7				
		10	20.0	0.67	44.7				
27-2	0.16	20	60.0	1.13	7.1	93	100	100	100
		15	66.7	1.22	7.6				
		10	60.0	1.13	7.1				
		10	60.0	1.13	7.1				
29-1	0.2	20	60.0	1.13	5.7	100	79	78	62
		15	60.0	1.13	5.7				
		10	40.0	0.89	4.5				
		10	80.0	1.45	7.3				
29-2	0.2	20	75.0	1.36	6.8	100	94	93	88
		15	75.0	1.36	6.8				
		10	70.0	1.27	6.4				
		10	80.0	1.45	7.3				
32-1	0.2	20	75.0	1.36	6.8	99	93	84	78
		15	73.3	1.33	6.7				
		10	80.0	1.45	7.3				
		10	60.0	1.13	5.7				
32-2	0.1	20	45.0	0.94	9.4	98	83	84	70
		15	46.7	0.96	9.6				
		10	60.0	1.13	11.3				
		10	30.0	0.79	7.9				
43-1	0.02	20	85.0	1.55	77.5	87	92	94	86
		15	93.3	1.78	89.0				
		10	90.0	1.68	84.0				
		10	80.0	1.45	72.5				
52-1	0.02	20	45.0	0.94	47.0	90	95	94	89
		15	53.3	1.04	52.0				
		10	40.0	0.89	44.5				
		10	50.0	1.00	50.0				

In this study, 43 cases had determinations of both estrogens and gonadotropins and 14 had only estrogen determinations. Whenever possible two consecutive twenty-four-hour specimens were obtained. In general each specimen was assayed separately but occasionally the two specimens were pooled before assay. Two extracts were made for each specimen and 20 rats were used for each pharmacologic assay. Thus a two-day assay value for estrogen is the result of the use of approximately 90 rats. It was not always possible to determine gonadotropin on both specimens. When both assays were made on both specimens the values used in the statistical study were the averages of the two days; when gonadotropin was not determined on the second specimen the estrogen determination on the second day was omitted. This procedure was followed because of its bearing on the estrogen-gonadotropin ratio discussed later. The twenty-four-hour urine volumes were calculated for the eclamptic patients. The unabridged data are shown in Table III.

1. Classification

Group A.—This group corresponds to the group A of the classification of the American Committee on Maternal Welfare[16] and consists of 14 patients with hypertensive and renal disease in whom the disease was not peculiar to pregnancy but aggravated by it. It was not subdivided into Group I and II. Table IV. The week of pregnancy ranged from 31 to 40 (average, 35.1 weeks).

Group B.—This group corresponds to Group B of the classification of the American Committee and consists of toxemic patients in whom the disease was dependent upon pregnancy or peculiar to it. Group BI consists of 13 preeclamptic patients; the week of pregnancy ranged from 29 to 38 (average 34.3 weeks), and Group BII of five eclamptic patients ranging from twenty-nine to forty-four weeks of pregnancy (average 38.2 weeks) (Table IV).

Group C.—This group consists of 11 patients hospitalized pending cesarean section or because of mild cardiac disease. This group was used as a control group (Table IV). This group ranged from twenty-eight to forty weeks of pregnancy (average, 34.9 weeks).

2. Excretion of Estrogen

The excretion of estrogen varied greatly in each group of patients. Although there was in general a low excretion in the pre-eclamptic and eclamptic patients, the overlapping of values made it difficult, unless a value was extreme, definitely to assign it to any group (Fig. 3). The excretion per cubic centimeter is found in Tables III and IV. The twenty-four-hour excretion values expressed in I.U. per twenty-four hours range from 15,150 to 65,150 in the normal group (Group C), from 6,850 to 78,400 in the hypertensive and renal disease group (Group A), from 2,500 to 34,350 in the pre-eclamptic group (Group BI), and from 5,000 to 22,800 in the eclamptic group (Group BII) (Table IV, Figs. 3, 4, and 5). The estrogen excretion, I.U. per twenty-four hours, in the various groups expressed as the mean ± S.E. was as follows: Normal group, 38,260 ± 5,240; hypertensive and renal disease group, 37,540 ± 5,770; pre-eclamptic group, 17,620 ± 3,030; eclamptic group, 11,800 ± 3,670. The lowered excretion of estrogen in pre-eclampsia and eclampsia is in agreement with most investigators. However, no attempt can be made to compare the quantitative values of various workers[1-13, 15, 36-54, 64, 65] because of the different methods of assay and also of extractions employed in different laboratories.

Since any extreme value may greatly effect a mean value, it seemed advisable to subject these data to statistical analysis in order to determine the significances of the differences observed in the excretion in the various groups. Fisher's method[55] of testing the significance between two means was used. The difference between the estrogen excretion in the normal and the hypertensive and renal disease groups was not significant ($P = > 0.9$), but the differences observed between the normal and the pre-eclamptic or combined pre-eclamptic and eclamptic, the normal and eclamptic, and the pre-eclamptic and hypertensive renal disease groups were significant ($P = < 0.01$). There is less than one chance per 100 that differences such as observed between the normal and the pre-eclamptic group could have been obtained by chance from another group

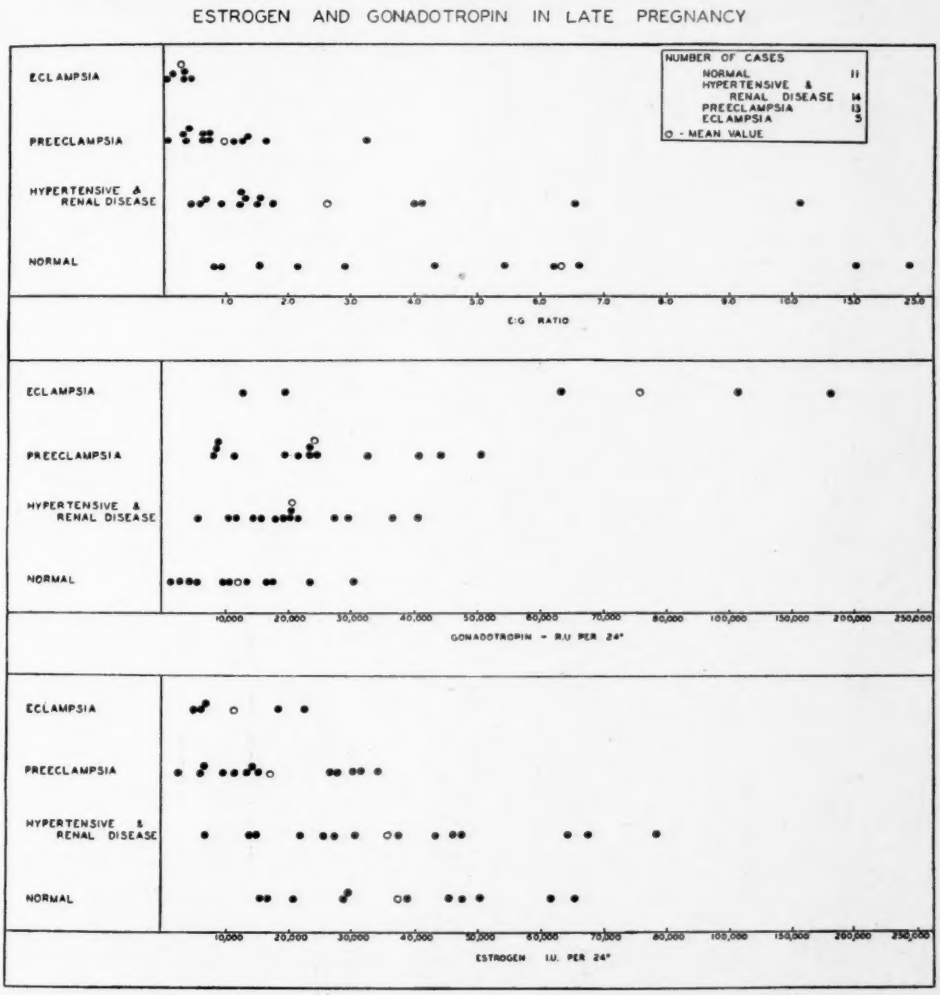

Fig. 3.

of "normal" patients and also that there was less than one chance per 200 that a mean as low as that found in the pre-eclamptic could have been obtained by chance in another group of "normal" patients. There was a significant difference between the estrogen excretion in the pre-eclamptic and hypertensive and renal disease groups ($P = < 0.01$).

TABLE III. EXCRETION OF ESTROGENS AND GONADOTROPINS IN LATE PREGNANCY

SPEC. NO.	WK. PREG.	24° VOLUME	ESTROGENS†				GONADOTROPINS			E:G RATIO
			NO. PREPARATIONS	NO. RATS	I.U. PER C.C.	I.U. PER 24°	NO. RATS	R.U. PER C.C.	R.U. PER 24°	
Group A. Hypertensive and Renal Disease										
25-1	37	1285	2	40	61.0	78,400	26	15.2	19,500	4.01
30-1	33	1300	3	60	37.6	48,800	39	30.6	39,800	1.23
30-2		985	2	39	44.6	43,900	70	33.8	33,300	1.32
32-1	31	2975	2	40	27.9	83,000	21	6.1	18,700	4.57
32-2		1385	2	45	33.4	46,300	20	9.4	13,000	3.55
37-1	37	1805	2	40	25.6	46,200	24	1.7	3,100	14.77
37-2		1955	2	40	24.5	47,900	20	3.8	7,400	6.50
39-1	39	1200	2	40	21.4	25,700	14	26.0	31,200	0.82
39-2		1350	3	59	21.6	29,200	19	20.6	27,800	1.05
53-(1 & 2)*	37	2335	3	58	18.6	43,400	18	11.8	27,400	1.58
55-(1 & 2)	31	600	2	40	23.1	13,900	19	33.4	20,000	0.69
56-(1 & 2)	34	475	2	40	30.3	14,400	20	23.5	11,300	1.29
63-1	34	715	2	26	4.0	2,900	18	13.1	9,400	0.31
63-2		1590	3	41	6.8	10,800	20	12.0	19,100	0.57
65-1	34	1960	2	40	26.2	51,400	18	11.0	21,600	2.38
65-2		930	3	60	25.6	23,800	18	23.0	21,400	1.11
78-1	40	2075	2	40	11.7	24,300	19	22.3	46,400	0.52
78-2		1985	2	40	13.5	26,800	20	17.7	35,100	0.76
82-1	37	1510	2	42	16.2	24,500	20	9.4	14,200	1.72
82-2		1460	2	43	13.3	19,400	16	14.4	21,000	0.92
83-1	32	1930	2	40	16.7	32,200	17	10.9	21,000	1.53
83-2		2610	2	40	11.3	29,500	19	7.3	19,100	1.55
91-2	35	2460	1	20	27.3	67,200	12	4.2	10,200	6.58
91-3		1780	2	45	23.3	41,500				
49-1	36	2135	2	40	26.0	55,500				
49-2		2965	2	40	18.6	55,100				
85-1	26	250	2	44	43.3	10,800				
85-2		1800	2	40	17.0	30,600				
90-2	35	1900	2	40	23.3	44,300				
90-3		1430	1	20	29.4	42,000				
93-1	30	1285	2	40	29.2	37,500				
93-2		1365	2	40	24.8	33,900				
93-3		2160	2	40	18.8	23,700				
97-1	34	670	2	40	12.2	8,200				
Group BI. Pre-Eclampsia										
35-1	30	1900	4	58	3.2	6,100	32	4.4	8,300	0.73
35-2		1900	2	35	4.2	8,000				
35-3		2030	2	33	3.6	7,300				
35-4		2480	2	34	4.1	10,200				
36-1	37	855	2	40	42.7	36,500	19	26.8	22,900	1.59
36-2		815	2	40	22.9	18,700	32	31.7	25,800	0.72

*Parentheses denote that specimens were pooled before assay.
†Estrogen values are expressed in equivalents of crystalline estrone.

TABLE III—CONT'D

SPEC. NO.	WK. PREG.	24° VOLUME	ESTROGENS†				GONADOTROPINS			E:G RATIO
			NO. PREPARATIONS	NO. RATS	I.U. PER C.C.	I.U. PER 24°	NO. RATS	R.U. PER C.C.	R.U. PER 24°	
40-1	35	670	2	40	46.6	31,200	15	34.7	23,200	1.35
40-2		1055	2	40	39.3	41,500				
41-1	29	685	2	40	9.6	6,600	15	12.8	8,800	0.75
41-2		1070	2	40	10.9	11,700				
41-3		1030	2	40	10.9	11,000				
46-1	36	1600	2	40	9.0	14,400	18	7.0	11,300	1.28
64-1	33	1090	2	40	24.1	26,300	19	7.8	8,500	3.09
64-2		1485	2	45	18.6	27,600	16	5.4	8,000	3.44
66-1	29	1530	3	45	7.3	11,200	17	21.3	29,600	0.34
66-2		1660	2	40	7.1	11,800	18	21.8	36,200	0.33
67-1	31	1515	2	40	6.2	9,400	18	10.1	15,300	0.61
67-2		2450	3	60	8.2	20,100	23	12.7	31,100	0.65
72-1	38	925	2	40	38.0	35,200	20	19.2	17,800	1.98
72-2		720	2	40	34.9	25,100	21	28.2	20,300	1.24
77-1	36	2100	2	40	8.6	18,100	11	21.2	44,500	0.41
77-2		4250	2	39	11.9	50,600	20	13.3	56,500	0.89
89-2	36	575	3	45	4.3	2,500	20	77.5	44,600	0.06
89-3		800	4	46	4.2	3,400				
94-1	38	685	3	50	19.7	13,500	19	61.2	41,900	0.32
94-2		800	2	40	7.5	6,000				
101-1	38	550	2	40	17.3	9,500	10	39.5	21,700	0.44
101-2		1300	2	40	17.0	22,100				
86-1	37	1120	2	45	12.8	14,300				
86-2		2205	2	40	13.5	29,800				
92-1	42	1090	3	56	4.5	4,900				
100-1	35	1300	1	20	6.3	8,200				
100-2		2000	2	40	5.9	11,800				
102-1	40	1800	2	40	15.3	27,500				
102-2		3600	2	40	11.0	39,600				
103-1	37	1900	2	40	17.8	33,700				
103-2		3200	2	40	13.1	41,800				
104-1	35	800	2	40	14.0	11,200				
104-2		1650	2	40	13.1	21,600				
106-1	35	1070	1	33	2.1	3,500				
106-2		2265	1	13	2.7	4,800				
Group BII. Eclampsia										
42-1	44	2900*	2	40	7.9	22,800*	14	21.8	63,200*	0.36
43-1	40	2340	4	48	2.1	5,000	20	77.5	181,400	0.03
47-1	43	2120	4	37	2.8	6,000	32	6.0	12,800	0.47
80-1	29	1560	2	37	11.9	18,400	17	69.0	107,600	0.17
96-1	35	1060	2	45	6.4	6,800	17	18.3	19,300	0.35

*Twenty-four-hour volumes calculated.
†See footnote at beginning of table.

TABLE III—CONT'D

SPEC. NO.	WK. PREG.	24° VOLUME	ESTROGENS†				GONADOTROPINS			E:G RATIO
			NO. PREPARATIONS	NO. RATS	I.U. PER C.C.	I.U. PER 24°	NO. RATS	R.U. PER C.C.	R.U. PER 24°	
Group C. Normals										
27-1	37	870	2	45	72.5	63,100	39	4.2	3,600	17.34
27-2		650	3	75	93.4	60,700	20	7.1	4,600	13.23
29-1	34	1450	2	45	40.1	58,100	20	5.7	8,200	7.10
29-2		1695	2	45	42.6	72,200	20	6.8	11,500	6.26
33-1	35	2960	3	75	19.4	57,400	22	10.0	29,600	1.94
33-2		2370	2	40	18.0	42,700	18	7.7	18,200	2.34
44-1	31	3645	3	59	10.7	39,000	19	0.5	1,600	23.78
44-2		3660	2	41	14.7	53,800				
59-(1 & 2)	28	935	2	45	18.1	16,900	21	2.9	2,700	6.24
61-(1 & 2)	39	500	2	40	41.6	20,800	11	26.5	13,300	1.57
62-(1 & 2)	40	370	3	60	80.4	29,700	20	14.8	5,500	5.43
69-1	40	2270	2	40	21.2	48,100	20	6.8	15,400	3.12
69-2		2460	2	40	19.3	47,500	20	7.2	17,700	2.68
73-1	40	665	3	65	32.1	21,300	20	37.7	25,100	0.85
73-2		1150	2	40	31.9	36,700	16	31.0	35,700	1.03
79-1	29	1605	2	50	10.7	17,200	23	11.1	17,800	0.96
79-2		910	2	40	14.3	13,000	20	18.8	17,100	0.76
81-1	31	435	2	40	75.5	32,800	16	21.6	9,400	3.50
81-2		850	3	65	68.4	58,100	15	13.3	11,300	5.14
98-1	39	775	2	40	39.2	29,300				
98-2		950	2	40	31.3	29,700				
107-1	38	2235	2	40	9.5	21,000				
107-2		865	2	40	15.8	13,700				
107-3		4470	2	40	4.8	21,900				
Group D. Miscellaneous‡										
87-1	40	1630	2	40	85.4	139,200	12	17.3	28,200	4.94
87-2		760	2	70	81.6	62,000				
71	39	675	2	40	63.7	43,000	18	22.8	15,400	2.79
28	36	2700	2	40	48.0	129,600	10	8.9	24,000	5.39
88	39	340	1	20	25.7	8,700				
22	14	820	2	50	13.6	11,200	20	68.0	55,800	
50	31	333	2	52	32.0	10,700	31	15.2	50,600	0.21
76	30	1515	2	38	5.0	7,600	20	2.7	4,000	1.89
105-1	37	850	2	40	32.7	26,800				
105-2		1400	2	40	31.0	43,400				
105-3		550	2	40	33.8	18,600				

‡Classification of cases: Cases 22 and 50 hyperemesis gravidarum; Case 23 diabetes mellitus; Cases 28 and 88 epilepsy; Case 35 abruptio placentae; Cases 45, 54, 58 hypertensive and renal disease; Case 51 diabetes insipidus; Case 71 edema; Case 75 hysteria, polyhydramnios, partial separation of placenta; Case 76 death of fetus; Case 87 mild pre-eclampsia; Case 95 achondroplastic dwarfism; Case 105 placenta previa; Case 108 pseudomucinous cystadenoma of the ovary.

TABLE III—CONT'D

SPEC. NO.	WK. PREG.	24° VOLUME	ESTROGENS†				GONADOTROPINS			E:G RATIO
			NO. PREPARATIONS	NO. RATS	I.U. PER C.C.	I.U. PER 24°	NO. RATS	R.U. PER C.C.	R.U. PER 24°	
35-(8&9)**	32	2780	2	42	3.6	10,000				
75-1	37	4520	2	42	19.5	88,100	20	9.5	41,800	2.11
75-2		4790	3	85	20.7	99,200	20	6.0	28,700	3.45
95-1	38	2150	2	42	15.9	34,200				
95-2		1430	2	40	22.6	32,300	14	23.0	32,900	0.98
95-3		2670	2	40	20.5	54,700				
23-1	37	800	2	40	141.5	113,200	15	48.8	39,000	2.90
51-1	37	6700	2	39	9.5	63,700				
51-2		5480	1	20	9.6	52,600				
51-(6&7)**		6025	3	60	16.4	98,800	18	0.8	4,600	21.58
108-1	31	710	2	40	13.5	9,600				
108-2		530	2	40	19.7	9,400				
108-3		1690	2	40	9.1	15,400				
45-1	23	2170	2	22	1.1	2,400				
45-2		3530	1	9	1.2	3,500				
54-(1&2)**	24	790	2	40	12.0	9,500	20	5.9	4,700	
58	10	1620	2	35	3.4	5,500	22	16.3	26,400	

**(1 & 2) denotes average of 2 specimens. (6 & 7) (8 & 9) denotes pooled specimens.

3. EXCRETION OF GONADOTROPIN

The excretion of gonadotropin was determined on the same groups of patients described above (Table IV). In each group the variation was great and values in each group overlapped those of other groups. (Fig. 3). The concentration per cubic centimeter is found in Tables III and IV. The range of the gonadotropin values varied in the normal group (Group C) from 1,600 to 30,400, in the hypertensive and renal disease group (Group A), from 5,250 to 40,750, in the pre-eclamptic group (Group BI), from 8,250 to 50,500, and in the eclamptic group (Group BII) from 12,800 to 181,400 R.U. per twenty-four hours (Table IV). The mean values (Mean ± S.E.) for these groups were: normal group, 12,340 ± 2,760; hypertensive and renal disease group, 20,690 ± 2,660; pre-eclamptic group, 24,470 ± 3,960; eclamptic group, 76,860 ± 31,210 R.U. per twenty-four hours. Comparison of these means by the Fisher method[55] showed a significant difference between the excretion of gonadotropin in the normal and pre-eclamptic groups ($P = 0.03$), the normal and the eclamptic groups ($P = < 0.01$), the normal and combined pre-eclamptic and eclamptic groups ($P = < 0.06$), the normal and the hypertensive and renal disease groups ($P = 0.04$), but no difference between the pre-eclamptic and hypertensive and renal disease group ($P = 0.43$). Because of lack of uniformity of standards in various laboratories no attempt can be made to compare these values with those of other workers.[1-3, 5, 8, 15, 36, 37, 39, 45, 52, 56-63]

4. ESTROGEN-GONADOTROPIN RATIO

The individual variation in the excretion of either estrogen or gonadotropin is extreme and the standard deviation in any group may be larger than an individual value in the group. In general, it seemed that

in individual cases there was a relationship between the amount of estrogen and gonadotropin excreted, i.e., when the estrogen was high the gonadotropin also tended to be high (Fig. 4). This observation led to the calculation of the estrogen-gonadotropin ratio which is an arbitrary value dependent upon the units chosen to express both estrogen and gonadotropin. These E:G ratios (estrogen to gonadotropin ratio) ranged as follows: normal group (Group C), 0.86 to 23.78; hypertensive and renal disease group (Group A), 0.44 to 10.64; pre-eclamptic group (Group BI), 0.06 to 3.27; and the eclamptic group (Group BII), 0.03 to 0.47. The mean E:G ratio values (Mean ± S. E.) for the various groups were: normal, 6.38 ± 2.13; hypertensive and renal disease, 2.63 ± 0.77; pre-eclamptic, 0.97 ± 0.23; eclamptic, 0.28 ± 0.08. Considered statistically, there was a significant difference between the means of the normal and the pre-eclamptic groups ($P = 0.01$) but the mean of the hypertensive and renal disease group fell between these two groups and showed only a borderline significance to each group ($P = 0.07$ and $P = 0.06$, respectively). That is, there were approximately 3 chances per hundred that a mean ratio of another group of similar patients would fall within the range of the normal group or that of the

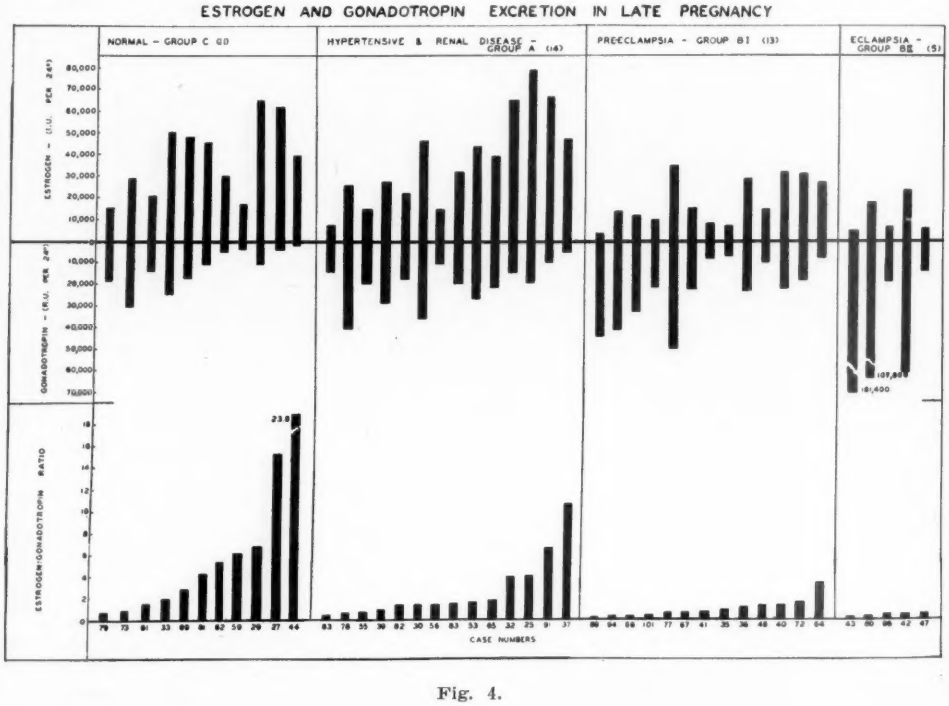
ESTROGEN AND GONADOTROPIN EXCRETION IN LATE PREGNANCY
NORMAL - GROUP C (80)
HYPERTENSIVE & RENAL DISEASE - GROUP A (16)
PREECLAMPSIA - GROUP BI (13)
ECLAMPSIA - GROUP BII (5)
ESTROGEN - (I.U. PER 24H)
GONADOTROPIN - (R.U. PER 24H)
ESTROGEN/GONADOTROPIN RATIO
23.8
CASE NUMBERS

Fig. 4.

pre-eclamptic group. Comparison by the Fisher method of the normal and the eclamptic groups showed no significant difference ($P = 0.08$) between the means probably due to the small number in the eclamptic group (5) and the extreme range in values in the normal group. If the two extremely high ratios (which varied by more than twice the standard deviation of the mean) are omitted, which lowers the mean, and the difference between these means, the difference becomes significant ($P = < 0.01$). When the pre-eclamptic and eclamptic groups are com-

bined there is a significant difference ($P = < 0.01$) between this mean (0.78 ± 0.56) and that of the normal or of the hypertensive and renal disease group. It seems that the E:G ratio is a better index of hormone values in individual cases than the twenty-four-hour excretion value of either estrogen or gonadotropin. In the normal group, 9 of 11 ratios, and in the pre-eclamptic group only 2 of 13 were above 1.5. Furthermore, this value is independent of the twenty-four-hour urine volume and the accuracy of its collection. (Figs. 3, 4, 5.)

5. Further Observations on Excretion of Estrogen

Since it was not possible to do gonadotropin determinations on all patients and sometimes only on one specimen, the data on estrogen excretion are more complete. The data in this group represent the complete data on the twenty-four-hour estrogen excretion and consist of the 43

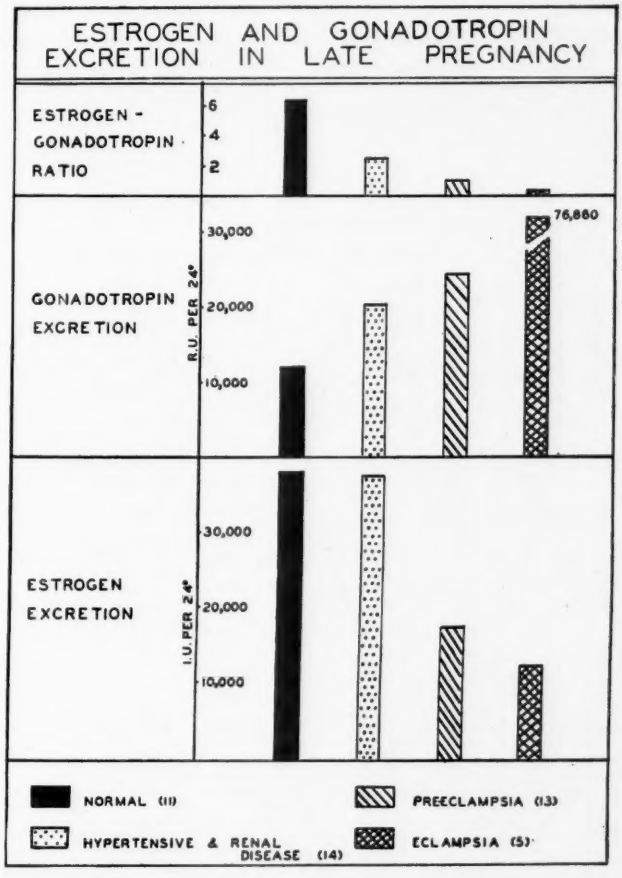

Fig. 5.

cases in groups discussed above and 14 other cases in which only estrogen was determined. In 32 cases the estrogen value was determined by averaging the assays of two consecutive specimens, in six cases pooled specimens and nine cases the value of only one specimen. Excluding the trial assay these values are based on approximately 3,000 tests. The twenty-four-hour excretion values varied in the normal group (13 cases)

TABLE IV. EXCRETION OF HORMONES IN LATE PREGNANCY

SPEC. NO.	ESTROGEN† I.U. PER C.C.	ESTROGEN†‡ I.U. PER 24 HOURS	GONADOTROPIN R.U. PER C.C.	GONADOTROPIN‡ R.U. PER 24 HOURS	E:G RATIO	24° VOLUME
Group A. Hypertension and Renal Disease						
25-1	61.0	78,400	15.2	19,500	4.01	1,285
30-1 & 2	41.1	46,350	32.2	36,550	1.28	1,143
32-1 & 2	30.7	64,650	7.8	15,850	4.06	2,180
37-1 & 2	25.1	47,050	2.8	5,250	10.64	1,880
39-1 & 2	21.5	27,450	23.3	29,500	0.94	1,275
53-(1 & 2)	18.6	43,400	11.8	27,400	1.58	2,335
55-(1 & 2)	23.1	13,900	33.4	20,000	0.69	600
56-(1 & 2)	30.3	14,400	23.5	11,300	1.29	475
63-1 & 2	5.4	6,850	12.6	14,250	0.44	1,153
65-1 & 2	25.9	37,600	17.0	21,500	1.75	1,445
78-1 & 2	12.6	25,550	20.0	40,750	0.64	2,030
82-1 & 2	14.8	21,950	11.9	17,600	1.32	1,485
83-1 & 2	14.0	30,850	9.1	20,050	1.54	2,270
91-2	27.3	67,200	4.2	10,200	6.58	2,460
N = 14						
Mean ± S. E.	25.10 ± 3.66	37,540 ± 5770	16.06 ± 2.53	20,690 ± 2,660	2.63 ± 0.77	1,573 ± 169
Group BI. Pre-eclampsia						
35-1	3.2	6,100	4.4	8,300	0.73	1,900
36-1 & 2	32.8	27,600	29.3	24,350	1.16	835
40-1	46.6	31,200	34.7	23,200	1.35	670
41-1	9.6	6,600	12.8	8,800	0.75	685
46-1	9.0	14,400	7.0	11,300	1.28	1,600
64-1 & 2	21.4	26,950	6.6	8,250	3.27	1,288
66-1 & 2	7.2	11,500	21.6	32,900	0.34	1,595
67-1 & 2	7.2	14,750	11.4	23,200	0.63	1,983
72-1 & 2	36.5	30,150	23.7	19,050	1.61	823
77-1 & 2	10.3	34,350	17.3	50,500	0.65	3,175
89-1	4.3	2,500	77.5	44,600	0.06	575
94-1	19.7	13,500	61.2	41,900	0.32	685
101-1	17.3	9,500	39.5	21,700	0.44	550
N = 13						
Mean ± S. E.	17.32 ± 3.74	17,620 ± 3,030	26.69 ± 6.12	24,470 ± 3,960	0.97 ± 0.23	1,259 ± 215

Group BII. Eclampsia						
42-1	7.9	22,800	21.8	63,200*	0.36	2,900
43-1	2.1	5,000	77.5	181,400	0.03	2,340
47-1	2.8	6,000	6.0	12,800	0.47	2,130
80-1	11.9	18,400	69.0	107,600	0.17	1,560
96-1	6.4	6,800	18.3	19,300	0.35	1,060
N = 5						
Mean ± S. E.	6.22 ± 1.79	11,800 ± 3,670	38.52 ± 14.48	76,860 ± 31,210	0.28 ± 0.08	1,998 ± 318
Group C. Normals						
27-1 & 2	83.0	61,900	5.6	4,100	15.29	760
29-1 & 2	41.4	65,150	6.2	9,850	6.68	1,573
33-1 & 2	18.7	50,050	8.9	23,900	2.14	2,665
44-1	10.7	39,000	0.5	1,600	23.78	3,645
59-(1 & 2)	18.1	16,900	2.9	2,700	6.24	935
61-(1 & 2)	41.6	20,800	26.5	13,300	1.57	500
62-(1 & 2)	80.4	29,700	14.8	5,500	5.43	370
69-1 & 2	20.3	47,800	7.0	16,550	2.90	2,365
73-1 & 2	32.0	29,000	34.4	30,400	0.94	908
79-1 & 2	12.5	15,150	15.0	17,450	0.86	1,258
81-1 & 2	72.0	45,450	17.5	10,350	4.32	643
N = 11						
Mean ± S. E.	39.15 ± 8.26	38,260 ± 5,240	12.66 ± 3.13	12,340 ± 2,760	6.38 ± 2.13	1,420 ± 315

*Parentheses indicate that specimens were pooled before assay, 1 and 2 indicates average of 2 specimens.
†Estrogen values are expressed in equivalents of crystalline estrone.
‡Twenty-four-hour volume calculated.

from 15,150 to 65,150 I.U., in the hypertensive and renal disease group (19 cases) from 6,850 to 78,400, in the pre-eclamptic group (20 cases) from 2,950 to 37,850 I.U. and the eclamptic group (5 cases) 5,000 to 22,800 I.U. per twenty-four hours. The mean excretion values mean ± S.E. (I.U. per 24°), of the different groups were: normal, 36,550 ± 4,780; hypertensive and renal disease, 35,580 ± 4,490; pre-eclamptic, 18,490 ± 2,600; eclamptic, 11,800 ± 3,670. These differences, considered statistically,[55] show a significant difference between the estrogen excreted by the normal group and the pre-eclamptic group ($P = < 0.01$), and between the pre-eclamptic and hypertensive and renal disease groups ($P = < 0.01$), but not between the normal and the hypertensive and renal disease group ($P = 0.87$).

General inspection of the data on the excretion of estrogens on two consecutive days suggested that there was a tendency toward larger estrogen value in the larger twenty-four-hour volume. These data were arranged in two groups according to the smaller and larger volumes. In normal patients the group with smaller volumes excreted 35,870 ± 5,370 I.U. per twenty-four hours and with the large volumes the same patients excreted 45,670 ± 5,890 I.U. per twenty-four hours. This difference was not statistically significant ($P = 0.23$). Similarly in the hypertensive and renal disease group the excretion by the smaller volume group was 31,480 ± 4,020 I.U. and by the larger, 41,720 ± 5,100 I.U. per twenty-four hours, and the difference was not significant ($P = 0.13$). However, in the pre-eclamptic group the lower volume group excreted 15,370 ± 2,280 I.U. and the higher volume group 23,670 ± 3,470 I.U. per twenty-four hours. These differences gave a probability of 0.05, or 2.5 chances per 100 that a mean as high as that observed in the high volume group could have resulted by chance. It indicates that in pre-eclampsia there may be a kidney excretion factor for estrogens. Furthermore, in about 56 per cent of the normal patients, 43 per cent of the hypertensive and renal disease patients, and 78 per cent of the pre-eclamptic patients, the amount of estrogen in the lower of the two volumes was less than 80 per cent of that calculated on the basis of the excretion in the higher volume specimen. Such a kidney excretion factor has been suggested recently by Hain.[48]

III. Excretion of Estrogen and Gonadotropin in Other Pathologic Conditions of Pregnancy

Estrogen and gonadotropin excretion during pregnancy was determined in 17 additional cases not included in the above series; 4 cases were studied early in pregnancy and 13 cases presented a variety of different conditions. These data are found in Table III. The four cases of toxemia observed too early in pregnancy to be included in the above studies are reported merely for the benefit of other workers. In the other conditions complicating pregnancy no attempt has been made to evaluate the findings in respect to reports in the literature. In this group the ratios were high in patients without toxic symptoms except for the dwarf. Although it is unwise and difficult to evaluate individual cases a few suggestions follow:

In the mild pre-eclamptic (Case 87), both the estrogen and gonadotropin values were high and the E:G ratio was normal. There was one patient (Case 71) who showed no symptoms other than marked edema at the time the hormone determinations were made. The estrogen and gonadotropin excretion was normal at this time, and the ratio was normal. The patient later developed pre-eclampsia.

There were two cases of epilepsy in this group. In the mild case (Case 28) the estrogen and gonadotropin were both high and the ratio high. In the other case (Case 88), only estrogen was determined and was found to be low.

Two cases of hyperemesis gravidarum were studied. One case (Case 22) was early in pregnancy; the other case (Case 50) showed low estrogen and high gonadotropin with a resulting low E:G ratio. Only one case (Case 76) was studied in which the death of the fetus was the complicating condition. Both estrogen and gonadotropin were low and the ratio was low but normal.

Estrogen was normal in the one case of placenta previa (Case 105).

One patient was studied in two pregnancies. Data on her second pregnancy were included in Group BI. Her third pregnancy was complicated with partial separation of the placenta. At this time (30 weeks) the estrogen value was 10,000 I.U. per twenty-four hours; in the previous pregnancy (32 weeks) the estrogen ranged from 7,000 to 10,000 I.U. per twenty-four hours on four consecutive days. Both infants were stillborn.

In one case (Case 75) the pregnancy was complicated by hysteria, polyhydramnios, and partial separation of the placenta. Both estrogen and gonadotropin were high but the ratio was normal.

The excretion of estrogen was normal but the gonadotropin was high in an achondroplastic dwarf (Case 95). The ratio was low.

Both estrogen and gonadotropin were high in the patient (Case 23) in whom pregnancy was complicated by diabetes mellitus and hypertension. The ratio was normal.

In a case of diabetes insipidus (Case 51), the excretion of estrogen was high and the gonadotropin was very low; the ratio was high.

Estrogen excretion was low in a patient (Case 108) with a pseudomucinous cystadenoma of the ovary.

Conclusions

When the toxemias of pregnancy are classified according to the recommendations of the American Committee on Maternal Welfare, the twenty-four-hour excretion of estrogen and gonadotropin shows certain statistically significant differences between a group of normal patients and the groups with either pre-eclampsia and eclampsia in whom the disease is considered peculiar to pregnancy or with hypertensive and renal disease which existed before pregnancy or persisted after pregnancy. Extreme individual variation of the excretion of both estrogen and gonadotropin in all groups of patients was observed as reported by other workers. The variation persisted even with pharmacologic assay of the hormones. The mean values of the different groups show a lowered excretion of estrogen in the pre-eclamptic and eclamptic group but not in the hypertensive and renal disease group and an increased excretion in gonadotropin in the pre-eclamptic, eclamptic, and hypertensive and renal disease groups. These differences are statistically significant. It is impossible to evaluate the values obtained by different investigators because of the variation in technique of extraction and quantitative assay of the estrogen and gonadotropin.

There was extreme overlapping of the values of the different groups so that it is difficult unless a value is extreme to allocate it to a specific clinical group. In general there seemed to be a relationship between the amount of estrogen and gonadotropin excreted, that is, when the estrogen value was high the gonadotropin also tended to be high. This relationship has been expressed as the estrogen to gonadotropin ratio. In the different groups the mean ratio was lowest in pre-eclamptic and eclamptic groups, somewhat higher in the hypertensive and renal disease group and highest in the normal group. There was a significant difference between the normal and pre-eclamptic groups and a borderline difference between the hypertensive and renal disease group and either the normal or the pre-eclamptic group. When the pre-eclamptic and eclamptic groups are combined there is a significant difference between the mean ratio of this group and the hypertensive and renal disease group. This ratio for individual patients is a better index of hormone relationships than the twenty-four-hour excretion of either the estrogen or the gonadotropin. In pathologic conditions of pregnancy not showing toxic symptoms this ratio is normal in general.

From this study and others, it seems that estrogens and gonadotropins are in some way definitely associated with the toxemias of pregnancy. This work was not designed to contribute to the theories of the cause of toxemias but merely to substantiate certain findings pertinent to the relationship of these hormones to the toxemias. These results indicate a lowered excretion of estrogen and an increased excretion of gonadotropin in pre-eclampsia and eclampsia. There is an increase in gonadotropin only in hypertensive and renal disease. We realize that there is great individual variation in the excretion of these hormones and have attempted to offset this variation by use of the ratio of the estrogen to the gonadotropin excretion. Furthermore, a series of determinations on one patient might give a better evaluation of the hormonal state than a comparison of these values with those of other individuals. We are aware that hormone excretion is only a part of the general problem, and that a parallel study of the blood values is desirable. The question for the future seems to be to determine the cause of these hormonal changes whether or not they are attributable to changes in the production of these hormones, to disturbance of their ratios or to altered excretory, metabolic, and storage functions of the kidneys, liver, or placenta.

Summary

The excretion of estrogen and gonadotropin has been determined in 74 cases during pregnancy; 70 cases were studied during late pregnancy (thirty-five weeks) and 4 cases in early pregnancy. Of the 70 cases studied in late pregnancy, 57 cases were used for a statistical study of the relation of these hormones to the toxemias of pregnancy. Of these, 43 cases (11 normal, 14 hypertensive and renal disease, 13 pre-eclamptic,

and 5 eclamptic patients) had parallel quantitative assays of both estrogens and gonadotropins and 14 estrogen only. The other 13 cases represented various other conditions complicating pregnancy.

In the group (43 cases) in which both the estrogens and gonadotropins were determined, there was a decrease in the estrogen excretion and an increase in the excretion of gonadotropin in the pre-eclamptic and eclamptic groups, but the excretion of estrogen was normal and the excretion of gonadotropin increased in the hypertensive and renal disease group. Because of the extreme variability of individual values the relationship of the estrogen and gonadotropin excretions (E:G ratio) is believed to be a better index of hormone values than the twenty-four-hour excretion value for either hormone.

The values found for this group were:

1. The excretion of estrogen (Mean ± S. E., I.U. per 24 hours) for the various groups was: normal, 38,260 ± 5,240; hypertensive and renal disease, 37,540 ± 5,770; pre-eclamptic, 17,620 ± 3,030; eclamptic, 11,800 ± 3,670.
2. The excretion of gonadotropin (Mean ± S. E., R.U. per 24 hours) for the same groups was: normal, 12,340 ± 2,760; hypertensive and renal disease, 20,690 ± 2,660; pre-eclamptic, 24,470 ± 3,960; eclamptic, 76,860 ± 31,210.
3. The ratios of the excretion of estrogen to gonadotropin expressed as the Mean ± S. E., for the above groups were: normal, 6.38 ± 2.13; hypertensive and renal disease, 2.63 ± 0.77; pre-eclamptic, 0.97 ± 0.23; eclamptic, 0.28 ± 0.08.

Comparisons of these means by the Fisher method gave the following probabilities, P,* for significant differences between the various groups:

1. For the excretion of estrogen per twenty-four hours, these values for the different groups were: normal and pre-eclamptic, $P = < 0.01$; normal and hypertensive and renal disease, $P = > 0.9$; pre-eclamptic and hypertensive and renal disease, $P = < 0.01$.
2. For the excretion of gonadotropin per twenty-four hours in the same groups, the values were: normal and pre-eclamptic, $P = 0.03$; normal and hypertensive and renal disease, $P = 0.04$; pre-eclamptic and hypertensive and renal disease, $P = 0.43$.
3. For the estrogen:gonadotropin ratios the values were: normal and pre-eclamptic, $P = 0.01$, including the eclamptic group, $P = < 0.01$; normal and hypertensive and renal disease, $P = 0.07$; pre-eclamptic and hypertensive and renal disease, $P = 0.06$; hypertensive and renal disease and pre-eclamptic and including the eclamptic group, $P = < 0.01$.

The total group of estrogen studies (43 cases above and 14 with estrogen determinations only) gave the following values (Mean ± S. E., I.U. per 24 hours) for the various groups: normal, 36,550 ± 4,780; hypertensive and renal disease, 35,580 ± 4,490; pre-eclamptic, 18,490 ± 2,600. Comparison of these means shows a significant difference between the normal and the pre-eclamptic groups ($P = < 0.01$) and the pre-eclamptic and the hypertensive and renal disease groups ($P = < 0.01$) but not between the normal and the hypertensive and renal disease groups ($P = 0.87$).

*P = ±0.01 indicates one possibility in 100 that these differences are not significant.

Methods for the quantitative assay of estrogens and gonadotropins employing dose-effect standardization curves and methods of extraction are described and discussed.

Excretion of estrogen and gonadotropin has been studied in 17 additional cases representing the following conditions: early pregnancy, hyperemesis gravidarum, abruptio placentae, hysteria with polyhydramnios and partial separation of the placenta, epilepsy, death of fetus, diabetes insipidus, diabetes mellitus, edema, achondroplastic dwarfism, and pseudomucinous cystadenoma of the ovary.

We are indebted to Drs. Carl Huber and Louise Clancy for assistance in collecting and reviewing the clinical material.

References

1. Smith, G. V., and Smith, O. W.: Proc. Soc. Exper. Biol. & Med. **30**: 918, 1933.
2. Idem: Am. J. Physiol. **107**: 128, 1934.
3. Idem: Surg., Gynec. & Obst. **61**: 27, 1935.
4. Idem: Am. J. Physiol. **112**: 340, 1935.
5. Smith, O. W., and Smith, G. V.: Am. J. Obst. & Gynec. **33**: 365, 1937.
6. Smith, G. V., and Smith, O. W.: Am. J. Obst. & Gynec. **36**: 769, 1938.
7. Smith, G. V., Smith, O. W., and Pincus, G.: Am. J. Physiol. **121**: 98, 1938.
8. Smith, G. V., and Smith, O. W.: Am. J. Obst. & Gynec. **38**: 618, 1939.
9. Smith, O. W., Smith, G. V., and Schiller, S.: Endocrinology **25**: 509, 1937.
10. Smith, G. V., and Smith, O. W.: Am. J. Obst. & Gynec. **39**: 405, 1940.
11. Smith, O. W., Smith, G. V., and Schiller, S.: J. Clin. Endocrinol. **1**: 461, 1941.
12. Smith, O. W., and Smith, G. V.: Ibid. **1**: 470, 1941.
13. Smith, G. V., and Smith, O. W.: Ibid. **1**: 477, 1941.
14. Watts, R. M.: Discussion note to Taylor and Scadron, Am. J. Obst. & Gynec. **37**: 963 and 983, 1939.
15. Taylor, H. C., Jr., and Scadron, E. N.: Ibid. **37**: 963, 1939.
16. Am. Committee on Maternal Welfare, The Mother **1**: 13, 1940.
17. Gallagher, T. F., Koch, F. C., and Dorfman, R. I.: Proc. Soc. Exper. Biol. & Med. **33**: 440, 1935.
18. Gallagher, T. F., Petersen, D. H., Dorfman, R. I., Kenyon, A. T., and Koch, F. C.: J. Clin. Investigation **16**: 695, 1937.
19. Coward, K. H., and Burn, J. H.: J. Physiol. **63**: 270, 1927.
20. D'Amour, F. E., and Gustavson, R. G.: J. Pharmacol. & Exper. Therap. **40**: 473, 1930.
21. Idem: Ibid. **57**: 472, 1936.
22. Hain, A. M., and Robson, J. M.: Ibid. **57**: 337, 1936.
23. Burn, J. H., and Elphick, G. K.: Quart. J. Pharm. & Pharmacol. **5**: 192, 1932.
24. Hoskins, W. H., Coffman, J. R., Koch, F. C., and Kenyon, A. T.: Endocrinology **24**: 702, 1939.
25. Burn, J. H.: Biological Standardization, 1937, Oxford University Press, p. 140.
26. Heller, C., Lauson, H., and Sevringhaus, E. L.: Am. J. Physiol. **121**: 364, 1938.
27. Cartland, G. F., and Nelson, J. W.: Am. J. Physiol. **122**: 201, 1938.
28. Gaensbauer, F., and Bradbury, J. T.: Endocrinology **24**: 867, 1939.
29. Sealey, J. L., and Sondern, C. W.: Endocrinology **26**: 813, 1940.
30. Deansley, R.: Quart. J. Pharm. & Pharmacol. **8**: 651, 1935.
31. Korenchevsky, V., Dennison, M., and Simpson, S. L.: Biochem. J. **29**: 2522, 1935.
32. Bischoff, F.: Am. J. Physiol. **114**: 483, 1936.
33. D'Amour, F. E., and D'Amour, M. C.: Endocrinology **26**: 93, 1940.
34. Report of the Conference Bulletin of Health Organization of the League of Nations **7**: 889, 1938. Quoted J. A. M. A. **113**: 2418, 1939.
35. Watts, R. M., and Adair, F. L.: Dieckmann, W. J., The Toxemias of Pregnancy, St. Louis, Mo., 1941, The C. V. Mosby Company, p. 209.
36. Aschheim, S., and Zondek, B.: Klin. Wehnschr. **7**: 1404, 1928.
37. Runge, H., Hartman, H., and Sievers, K.: Arch. f. Gynäk. **149**: 608, 1932.
38. Runge, H., and Diethelm, K.: Zentralbl. f. Gynäk. **57**: 2472, 1933.
39. Heim, K.: Klin. Wehnschr. **13**: 1614, 1934.
40. Cohen, S. L., Marrian, G. F., and Watson, M.: Lancet **1**: 674, 1935.
41. Schmulovitz, A. B., and Wylie, H. B.: J. Lab. & Clin. Med. **21**: 210, 1933.
42. Savage, J. E., and Wylie, H. B.: Am. J. Obst. & Gynec. **33**: 771, 1937.
43. Savage, J. E., Wylie, H. B., and Douglass, L. H.: Ibid. **36**: 39, 1938.

44. Goldberger, M. A.: Ibid. **33**: 1093, 1937.
45. Browne, J. S. L., Henry, J. S., and Venning, E. H.: J. Clin. Investigation **17**: 503, 1938.
46. Hain, A. M.: Edin. M. J. **45**: 678, 1938.
47. Idem: Quart, J. Exper. Physiol. **29**: 139, 1939.
48. Idem: J. Endocrinology **2**: 104, 1940.
49. Idem: Ibid. **3**: 10, 1942; Chem. Abst. **36**: 4577, 1942.
50. Møller-Christensen, E., and Pedersen-Bjergaard, K.: Acta obst. & gynec. Scandinav. **16**: 142, 1936.
51. Dingemanse, E., Laqueur, E., and Mühlbock, O.: Monatschr. f. Geburtsh. & Gynäk. **109**: 37, 1939.
52. Seigler, S. L.: J. Lab. & Clin. Med. **24**: 1277, 1939.
53. Chevallier, A., and Manuel, S.: Compt. rend. Soc. de biol. **132**: 521, 1939.
54. Bachmann, C.: Am. J. Obst. & Gynec. **42**: 599, 1941.
55. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, 1932, Oliver & Boyd, p. 114.
56. Murphy, D. P.: Surg., Gynec. & Obst. **56**: 914, 1933.
57. Bentivoglio, F.: Riforma méd. p. 24, 1933; Zentralbl. f. Gynäk. **58**: 1021, 1934.
58. Bourg, R., and Legrand, G.: Arch. internal. de méd. expér. **10**: 522, 1935.
59. Heim, K.: Monatschr. f. Geburtsh. u. Gynäk. **104**: 1, 1936.
60. Anselmino, K. J., and Hoffmann, F.: Ztschr. f. Geburtsh. u. Gynäk. **114**: 52, 1936.
61. Ehrhardt, C.: Klin. Wchnschr. **15**: 514, 1936.
62. Browne, J. S. L., and Venning, E. M.: Lancet **2**: 1507, 1936.
63. Schmidt, K.: Ztschr. f. Geburtsh. u. Gynäk. **116**: 56, 1937.
64. Kemp, T., and Pedersen-Bjergaard, K.: Endocrinologie **13**: 156, 1933.
65. Lu Ching Shan, Chinese M. J. **59**: 131, 1941.

PLASMA VITAMIN A AND CAROTENE OF THE NEWBORN INFANT*

With Consideration of Fetal-Maternal Relationships

Curtis J. Lund, M.S., M.D., and Marian S. Kimble, Ph.D.,
Madison, Wis.

(From the Department of Obstetrics and Gynecology and the Biochemical Laboratory, Department of Medicine, University of Wisconsin Medical School, and the State of Wisconsin General Hospital)

THE development of an accurate method suitable for clinical determinations of plasma vitamin A has opened the way for a reinvestigation of the vitamin A relationship between mother and infant. In this paper we shall present the normal vitamin A and carotene values for the cord blood of the newborn infant under normal conditions, under conditions of diminished maternal intake, and under conditions of excessive maternal intake of vitamin A. The maternal-fetal relationship of vitamin A and carotene and its bearing on the placental transmission of these substances will be considered.

Several studies reported during the past ten years have disclosed that the newborn infant differs from the adult in the amounts of vitamin A present in blood and tissues. It is well to remember that earlier workers were handicapped by intricacies and inaccuracies of a poorly understood procedure, therefore many of their detailed findings can be accepted only with reservations. As late as 1936 one of the competent investigators[1] admitted that technical difficulties were ac-

*Aided by a grant from the Wisconsin Alumni Research Foundation.

countable for his failure to find any vitamin A in some samples of cord blood, as well as some samples of adult blood.

In 1932, Dann[2] studied the placental transfer of carotene and vitamin A in pregnant rats and rabbits. He observed that the vitamin A content of the fetal rat liver was small and could not be increased by giving large doses of carotene to the mother, yet large quantities of vitamin A given for a considerable length of time did increase reserve stores of the maternal and fetal livers.[3] Ellison and Moore[4] assayed the livers of newborn infants and found from 14 to 17 units of vitamin per gram of tissue, whereas the normal adult liver yielded about 220 units per gram of tissue. At about the same time Wendt[1] was analyzing blood from the umbilical cord, he was able to recover small amounts of carotene and usually very small amounts of vitamin A, but frequently he found no vitamin A. Neuweiler[5, 6] worked concurrently but independently, and reported the presence of vitamin A in fetal organs (liver), but never did he find carotene, a fact which led him to believe the placenta impervious to the pro-vitamin. Gaehtgens[7-10] also regarded the placenta a partial or complete barrier, as he was able to find vitamin A in the blood of no more than 5 of 23 infants. Many of the maternal values were zero also, a type of result no longer found by improved methods of analysis. Carotene was present in all cases but the reported range of variation, as we now realize, was excessive.

The investigations of Clausen and McCoord[11] were important as regards carotene. They demonstrated that fetal plasma was consistently and significantly lower in carotene content than was maternal plasma. Furthermore, the plasma from the umbilical vein (containing blood flowing to the fetus) showed a greater concentration of carotene than did the plasma from the umbilical arteries (containing blood coming from the fetus). From the difference in these values the authors estimated that the fetus utilized about one milligram of carotene daily. In the same study the mean plasma vitamin A of 63 infants was found to be 12.8 "blue units" while the mean value for 32 mothers was 15.2 "blue units," a small difference. Data were not presented which correlated values for individual infants with those of their mothers, instead the authors confined their discussion to comparisons of mean values. The mean concentration of vitamin A was similar in umbilical venous blood and umbilical arterial blood, but individually some infants exhibited greater amounts of vitamin A in the arterial blood, others showed higher values in venous blood. Such individual variations, said the essayists, might be due to error of method or to transmission of vitamin A from the fetus to the placenta or vice versa.

Toverud and Ender[12] assayed the vitamin A content of livers from 47 premature infants and 50 mature infants. The average vitamin A content of livers from premature infants was greater than that of mature infants; however, the range of variation was great. When dietary history indicated maternal deficiency the vitamin A content of fetal livers was also low. When an excellent maternal dietary history was obtained, the fetal vitamin A was high. The carotene content of the fetal liver was always low.

Rehearsal of the data obtained from these several sources indicated few points of complete agreement. All agree that the infant is relatively low in vitamin A and carotene and many are of the opinion that the infant is lower than the mother. Some believe the placenta im-

pervious to carotene and others believe it impervious to vitamin A. Yet certain observers consider that carotene passes to the fetus and forms vitamin A. If a single generalization is permissible from these observations and opinions, it would be that values of vitamin A and carotene in the fetus are low compared to those of the mother, and this difference suggests some impedence in the placenta.

Procedures

Samples of blood for study were obtained at delivery in the following manner: As the infant was delivered the pulsating umbilical cord was immediately clamped and severed. Twenty-five milliliters of blood were quickly collected from the placental end of the umbilical cord. A small amount of potassium oxalate in the receptacle prevented coagulation. This specimen was a mixture of venous and arterial blood, although venous blood formed the major part of the sample, as the umbilical arteries are small and contract quickly after the cord is clamped. A 12 ml. sample of maternal blood was withdrawn from a vein immediately after the fetal sample was obtained.

Total carotene and vitamin A were determined in the plasma with the aid of the Evelyn photocolorimeter according to the technic described by Kimble,[13] which adapts to blood analysis the method of assay of the vitamin in oils published by Dann and Evelyn[14] in 1938. This method for the macrocolorimeter follows the general lines suggested by May in the same year for the microcolorimeter[15] and smaller amounts of plasma. Briefly, the method involves extraction of the plasma carotinoids with ethyl alcohol and petroleum ether, determination of the carotene from the amount of yellow color imparted to the ethereal extract, removal of this solvent so that the remaining material can be dissolved in chloroform, and the development of the standard Carr-Price reaction by the addition of antimony trichloride in chloroform. The reaction takes place with the tube of extract in the reading position of the colorimeter so that the light transmission at maximum density of the evanescent color can be easily and accurately determined. The results of the final reaction are corrected for the amount of color due to carotene, using the constant given by Dann and Evelyn[14] for this purpose.

Recent studies in which more successfully purified preparations of carotene and vitamin A have been available for colorimetric standards indicate that some of the older constants used in calculating the results of the chemical determination of these substances will need to be changed for increased accuracy. This probability was noted in a previous publication.[13] Thus, though the chemical procedure has become so well standardized that colorimetric readings yielded by a given vitamin-containing preparation can readily be duplicated from one laboratory to another, *interpretation* of the chemical findings in terms of units or weights of the vitamin represented still varies grossly in different hands, according to the form of calculation and expression chosen. These uncertainties involve the exact correction to be applied to the amounts of blue color formed by the carotene mixed with vitamin A in the Carr-Price reaction, and also the validity of various conversion factors that have been worked out for interchanging chemical, or "blue" units with actual weights of the vitamin, or with the biologic (International) units that were formerly the only acceptable standard of reference. Because the details of these various relation-

ships are still controversial, with most of the final answers still to be furnished, calculation formulas used in the present work have remained the same as those used earlier in the same laboratory, excepting that the vitamin A is now expressed as the more generally familiar International Units by means of conversion factors suggested for tentative use before. It is interesting that data from some other laboratories are now available for comparison. But in this connection it must be emphasized that in any work concerning vitamin A, *both* the technique of assay and the method of calculation of results must be uniform before comparisons among different sets of data can be attempted.

Accordingly, the values for vitamin A in the plasma of healthy nonpregnant women studied in this laboratory have been found to lie, for the most part, between 75 and 120 I.U. per cent. These nonpregnant controls represented essentially the same sort of population as did the mothers of the present study. The average value for 50 nonpregnant women was 96 I.U. per cent. Using the same technique and calculations, results for healthy females have averaged 95, 87, and 87 I.U. per cent in three other available reports.[16-18]

For carotene, the female controls in this laboratory varied from 95 to 350 gamma per cent (micrograms per 100 ml.) with an average level of 203 gamma per cent. Others have recorded average figures of 197[16] and 227[17] for their control groups of nonpregnant women.

The patients chosen for study represented a broad economic and social group. Some were indigent, some were private patients and some were of intermediate status. The patients were approximately evenly divided within the three groups. The dietary intake of vitamin A was roughly estimated by careful questioning, and it was found to be variable, but in general it followed economic and social factors. In certain instances large doses of vitamin A were administered to the pregnant women in the form of halibut liver oil.*

Results—Vitamin A

Values in the Newborn.—The plasma vitamin A values of the newborn were lower generally than those values considered normal for an adult. A series of 143 determinations were made on the plasma of normal infants delivered at term pregnancy. The lowest value recorded was 24 I.U. per 100 ml. of plasma and the highest was 79. This is in contrast to the total range of 65 to 165 I.U. per 100 ml. obtained in this laboratory for healthy nonpregnant adult women. On the basis of further evidence, values from 65 to 75 are now considered "borderline." The mean plasma vitamin A for the infants was 49 I.U. per 100 ml. with a standard deviation of 12.2 and a coefficient of variability of 25 per cent. Fig. 1 illustrates the frequency distribution of the entire series. Note that 55 of the 143 infants (39 per cent) were within the range of 40 to 50 I.U. per cent and the remainder were not distant from the mode. Seventy-five per cent (104 of the 143 infants) were within the range of 30 to 60 I.U. per cent.

Relationship of Fetus to Mother.—Evaluation of the correlation between the infants' vitamin A and mothers' vitamin A for the data as a whole indicates a simple correlation coefficient of 0.22 which might be significant for 143 observations. Further examination and subdivision of these data suggest that a spurious correlation has arisen from some extraneous reason. Hence the results probably do not represent a true

*Haliver oil furnished through courtesy of Abbott Laboratories.

correlation between the mother and infant, and this belief was substantiated by the appearance of a scattergraph (not included) which showed no gross evidence of correlation. The differences between mother and infant in magnitude and range of vitamin A values for the whole series are disclosed by the frequency distribution of Fig. 1.

Fig. 2 exhibits the individual maternal-fetal relationship of each pair arranged according to the ascending vitamin A values of the mother. The fetal values can be seen as a broad band extending across

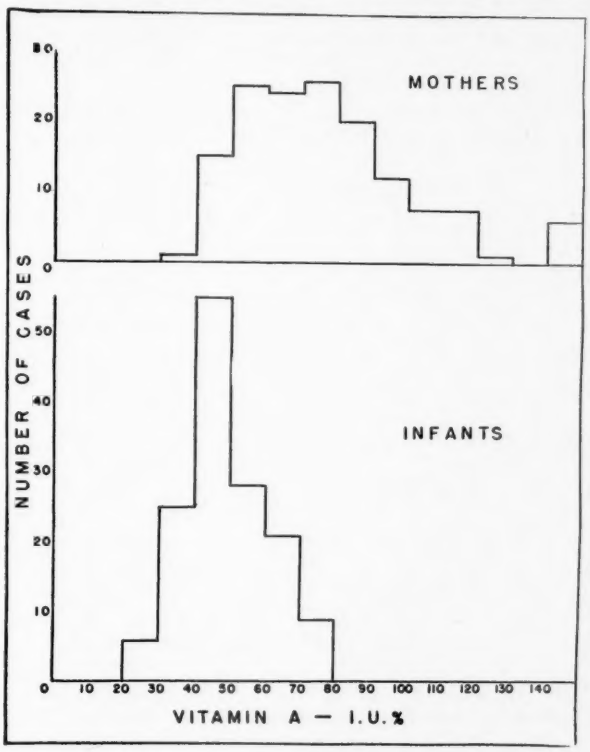

Fig. 1.—A frequency distribution graph showing the number of mothers and infants studied and the range of values of their plasma vitamin A.

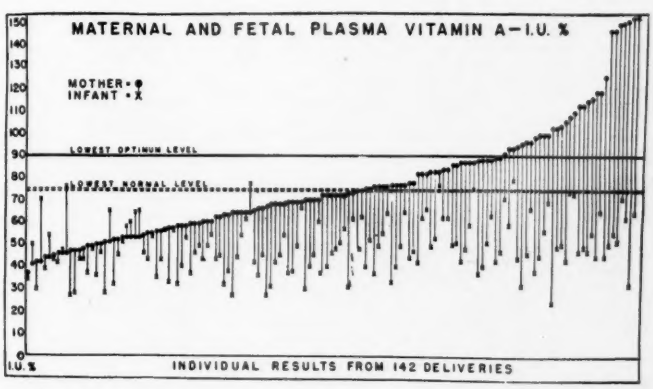

Fig. 2.—Showing the individual plasma vitamin A values for each mother and her infant. Note the presence of inverted relationships in the left half of the graph.

the entire field. Some of the highest fetal values are paired with the lowest maternal values and, conversely, some low fetal values accompany the highest maternal ones. The five highest infants had vitamin A values barely within the lower limits of what we consider a normal range for nonpregnant women; i.e., around 75 I.U. per 100 ml.

We have previously stated that under usual conditions the maternal values for vitamin A exceed those of the fetus. Further inspection of the data indicates this relationship was maintained as long as the mothers' vitamin A was normal. However, when the maternal values dropped below normal the fetal values were sometimes essentially equal to the mothers' and sometimes greater (Fig. 2). This upset we have called inversion. In the present study inversion appeared as maternal levels of vitamin A dropped below 80 I.U. per 100 ml. There were 91 mothers with vitamin A values below 80 I.U. per cent, and in 19 of these cases (21 per cent) there was inversion in the mother-infant vitamin A relationship. As the amount of maternal vitamin A decreased the frequency of inversion increased and there was "inversion" in eight cases with lowest maternal values.

When it became evident that the plasma vitamin A of the fetus remained independent of that of the mother, whether her plasma vitamin A was normal or below normal, we undertook to elevate the maternal values above normal by feeding large amounts of the vitamin during pregnancy. Moderate to large amounts of vitamin were given to nine patients for varying periods of time before parturition. Table I lists the dosages used, the duration of treatment, and the results obtained. Large doses of the vitamin elevated the maternal plasma concentration to a high level but they were without demonstrable effect on the fetus.

TABLE I.—SHOWING THE MATERNAL AND FETAL PLASMA VITAMIN A CONCENTRATION AFTER ADMINISTRATION OF MODERATE AND LARGE DOSES OF VITAMIN A

PATIENT	DAILY DOSE I.U.	DAYS OF TREATMENT	MATERNAL VITAMIN A BEFORE TREATMENT	MATERNAL VITAMIN A AT DELIVERY	FETAL VITAMIN A AT DELIVERY
MJ	20,000	98	*	76	55
BK	20,000	135	*	74	48
HJ	20,000	182	*	94	44
EF	30,000	210	*	148	52
CT	60,000	3	62	118	45
PW	60,000	12	86	113	55
MJ	60,000	32	58	149	62
DS	330,000	6	94	151	32
HS	330,000	18	72	145	55

*Comparison between values obtained early in pregnancy and values obtained at or near delivery is not permissible as will be shown in a forthcoming publication.

Miscellaneous Relationships.—Attempts were made to correlate the vitamin A of the newborn with numerous other variables apparent at birth.

A sex difference in adult plasma vitamin A has been pointed out by one of us (M. S. K.)[13] and has been verified[17, 18, 20] or independently noted[19] by others. These investigators have found the plasma vitamin A of the adult female to be lower than that of the adult male though all do not agree on the magnitude of the difference. We were interested to determine if a sex difference in vitamin A was present at birth. Of the 142 infants examined, 67 were females with a mean

plasma vitamin A of 52 I.U. per 100 ml., 75 were males with a mean value of 47 I.U. per cent. From these averages alone one might assume that there is a reversal in infants of the sex difference found in adults. However, the difference of the means is not statistically significant. Yet the data do show that the sex difference noted in adults does not obtain in the newborn infant. An explanation in adult physiology remains to be shown.

The amount of vernix caseosa was compared with the amount of plasma vitamin A. Suitable records of 65 infants permitted classification according to the amount of vernix caseosa. The amount of vernix caseosa was not accurately measured but experience quickly enabled us to divide the infants into one of the three groups: +, scanty amounts along the folds of the skin; ++, average amounts over body surfaces; and +++, large or excessive amounts. Table II indicates the findings:

TABLE II. A COMPARISON OF THE MEAN VITAMIN A CONCENTRATION IN PLASMA OF THE FETUS AND THE AMOUNT OF VERNIX CASEOSA PRESENT AT BIRTH

NUMBER OF INFANTS IN GROUP	AMOUNT OF VERNIX CASEOSA	MEAN VITAMIN A OF GROUP I.U. %
21	+	48
16	++	48
27	+++	49
	Mean for entire series	49

No correlation between vernix caseosa and amount of circulating vitamin A could be demonstrated and the average plasma vitamin A within each group was similar to the average for the series as a whole.

Five premature infants were studied. Data from so few infants are of little statistical value, yet it is interesting to note that premature infants had values for vitamin A which were below the group average and 3 of the infants were in the low range (Table III).

TABLE III. VITAMIN A, I.U. PER 100 ML. OF PLASMA IN PREMATURE INFANTS

WEIGHT IN POUNDS	GESTATIONAL AGE IN WEEKS	SEX	PLASMA VITAMIN A
2.5	26	M	37
3.0	32	F	37
3.8	34	M	34
4.0	30	M	46
4.7	30	F	47

The low vitamin A values for premature infants suggested the possibility of a relationship between maturity and vitamin A. Accurate determination of gestational age is exceedingly difficult; nevertheless, birth weight and gestational age are generally related, hence the birth weight and plasma vitamin A have been compared. A total of 147 infants were studied, including the 5 premature infants. Inspection of the data (Fig. 3) indicates some relationship between weight and vitamin A so long as the weight is below average. For example, not a single infant weighing 6½ pounds or less had a plasma vitamin A above 49 I.U. per 100 ml. The latter figure incidentally is also the mean for the entire series. The average weight of all infants was 7.5 pounds and the series was then subdivided according to weight, those above the average and those below it. Table IV summarizes the sta-

TABLE IV. STATISTICAL DATA COMPARING INFANT'S WEIGHT AND PLASMA VITAMIN A VALUES

	NUMBER OF INFANTS	MEAN VITAMIN A	MEAN WEIGHT IN POUNDS	S.D. WEIGHT	S.D. VITAMIN A	COEFFICIENT OF CORRELATION
Above 7.4 pounds	76	52	8.3	±0.63	±13	0.18
Below 7.4 pounds	71	45	6.4	±0.95	±10.5	0.28

tistical data for each weight group. Thus it would seem that low vitamin A values are related to a low birth weight, or possibly to some element associated with low birth weights.

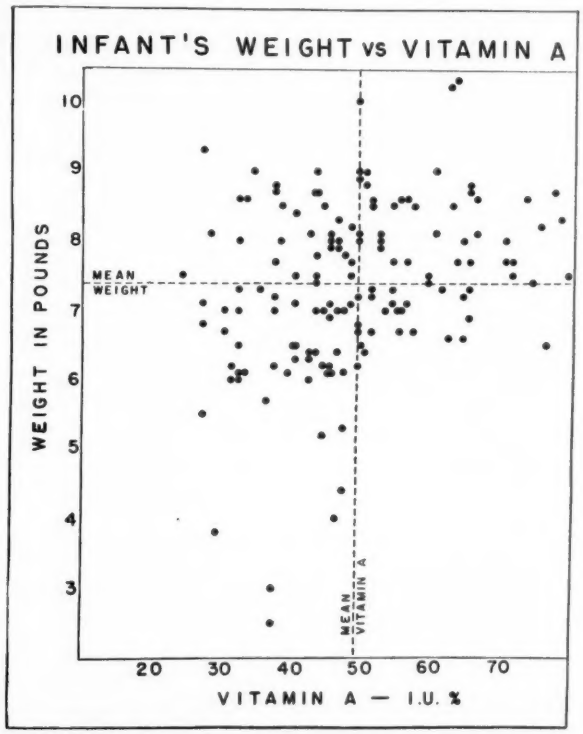

Fig. 3.—Showing the infants' weight plotted against plasma vitamin A. Note that all infants weighing less than 6½ pounds have plasma vitamin A values in the lower range.

Plasma vitamin A determinations were made on two sets of twins. A pair of identical twins had plasma vitamin A values of 30 and 71 I.U. per cent while nonidentical twins had values of 31 and 44 I.U. per cent. Such astonishing differences were not anticipated, particularly those of the identical twins. Obviously there was not complete and free exchange of blood between the identical twins; dissection of the placental vessels revealed the presence of anastomoses between small vessels only. These wide variations noted in infants supplied from an identical source lead us to believe that some intrinsic factor of the fetus may determine the concentration of plasma vitamin A. As we shall see in a subsequent paragraph, chemical dissimilarities between twins are not limited to vitamin A.

The scope of this study does not include abnormal infants, yet the striking results from one such infant warrants mention, though no explanation is at hand. This infant was delivered at term and seemed normal. An unusually small layer of red blood cells in the centrifuged specimen of cord blood clearly indicated the presence of a severe anemia. The plasma, which was proportionately increased, had a vitamin A value of 104 I.U. per 100 ml., a value 25 per cent higher than any other in our infant records. The infant, which survived, was found to have erythroblastosis of the anemic type.

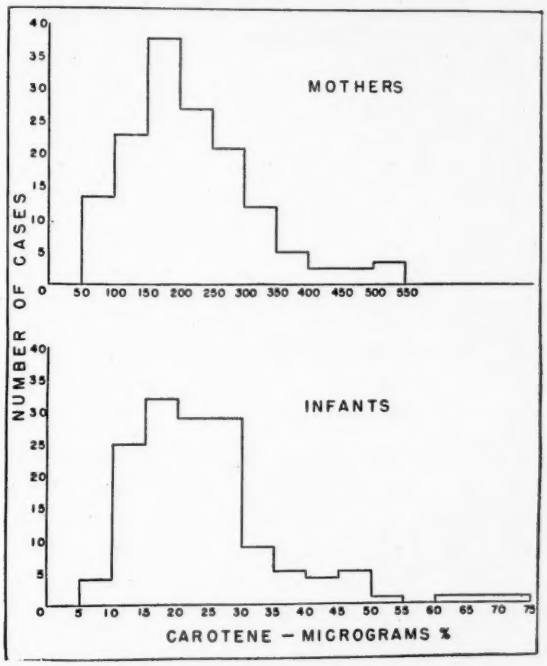

Fig. 4.—A frequency distribution graph showing the number of mothers and infants studied and the range of their plasma carotene. The scale of maternal values is ten times greater than the scale of fetal values.

Carotene

Values in Newborn Infants.—The plasma carotene of the cord blood is very low. The mean value for 149 normal infants delivered at term was 23 micrograms per 100 ml. of plasma, the lowest value recorded was 9 and the highest was 75. S.D. was 11.1 micrograms and the coefficient of variability was 48 per cent. Fig. 4 shows the frequency distribution of the entire series for the infants and their mothers. Note that the disparity in absolute levels of the two series is so great that the maternal values have been plotted on a scale ten times that for the infants. One hundred and fourteen of 149 infants (76 per cent) had carotene values between 10 and 30 micrograms per cent, which is roughly within $\pm 1 \times$ S.D. and indicates a "normal" type of distribution. Distribution in the maternal series appears "normal." The atypical high values to the right in both series represent mothers on high carotene intake.

Fig. 4 shows the frequency distribution of maternal and fetal values. For reasons mentioned in the preceding paragraph, the fetal values are

on a scale of one-tenth the maternal values in order to get a comparable plot. The shape of the curve of maternal values appears to be more "normal" than the curve of fetal values, but this could be explained by the difference in scale. Inherent error of our method for the determination of carotene is on the order of ±2 micrograms per 100 ml. Such a small error would not change the distribution of maternal values significantly, but it might well change the distribution of fetal values where the difference between groups is only 5 micrograms.

Miscellaneous Relationships.—The fetal carotene values and the fetal-maternal relationships did not deviate significantly under conditions of prematurity or multiple pregnancy.

Relation of Vitamin A and Carotene.—Carotene is the precursor of vitamin A and can be converted into vitamin A by the human body. The relationships between these two substances in the adult are complex and no correlation between the two can be demonstrated in human plasma.[13] In case the situation might be simpler in the infant, an effort was made to determine any relationship which might exist between carotene and vitamin A in the fetal plasma and this comparison was possible in a series of 133 cases. Correlation was lacking, as was the case with adults. This is demonstrated in Fig. 6. For example, it is possible to find low plasma vitamin A associated with either high or low plasma carotene, and conversely, a high plasma vitamin A might be combined with either high or low plasma carotene.

Discussion

Vitamin A.—The data from this study indicate that the normal infant is born with an exiguous supply of blood vitamin A, exiguous in the sense that a normal infant at birth has less vitamin A circulating in the blood than does its normal mother. This relationship extends to the tissues as well, for the fetal liver contains less vitamin A than the maternal liver.[4] Nevertheless, these low concentrations of vitamin A do not necessarily signify deficiency; rather they will need to be considered as the physiologic condition of the newborn infant.

The mode of the present series was from 40 to 50 I.U. per 100 ml. and included approximately 40 per cent of all infants, while a range of 30 to 70 I.U. per cent included approximately 90 per cent of all infants. For purposes of comparison the range of normal adult female values, as we have said, lies between 75 and 120 I.U. per cent. So long as the mother remains within this range her fetus may be expected to have values approximately one-half as high.

Relationship of Fetus to Mother.—In spite of the very low fetal plasma carotene it has a demonstrable direct relation to maternal carotene. Fig. 5 shows the fetal values plotted against the corresponding maternal values. Correlation is obvious by inspection alone. The multiple correlation coefficient of the entire series was 0.71, which appears to be highly significant. By statistical criteria, a somewhat curvilinear regression was found to describe the series slightly better than a straight line, and the following formula was derived: $IC = 4.06 + 0.0636\ MC + 0.0001\ MC^2$. When the values for maternal carotene, MC, are known, corresponding values for the infant, IC, can be estimated by the above formula. As a convenient rule of thumb the

fetal value may be estimated as one-tenth the maternal value, if the latter is within the middle range (Fig. 5). If maternal values fall in the low range the fetus has approximately one-eighth as much carotene and when maternal values are high the fetus has about one-twelfth as much carotene.

There was no correlation between the values of maternal and fetal plasma vitamin A. This lack of correlation suggests that the amount

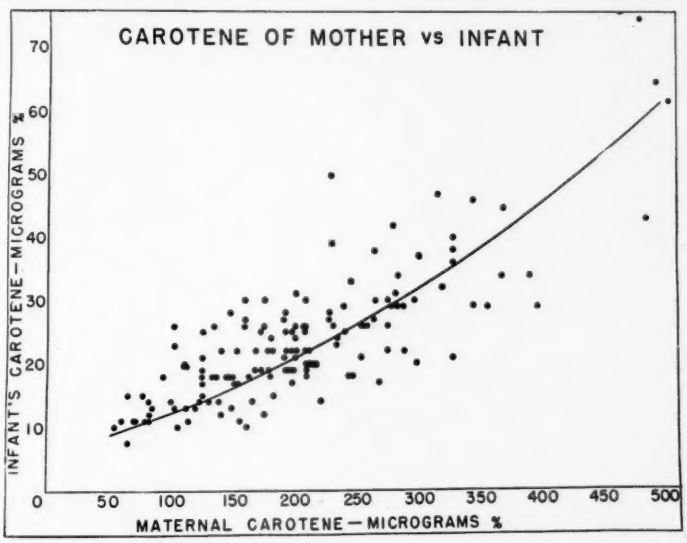

Fig. 5.—Scattergraph showing plasma carotene values of fetus plotted against the similar values for the mother. The line expresses the equation listed in the text.

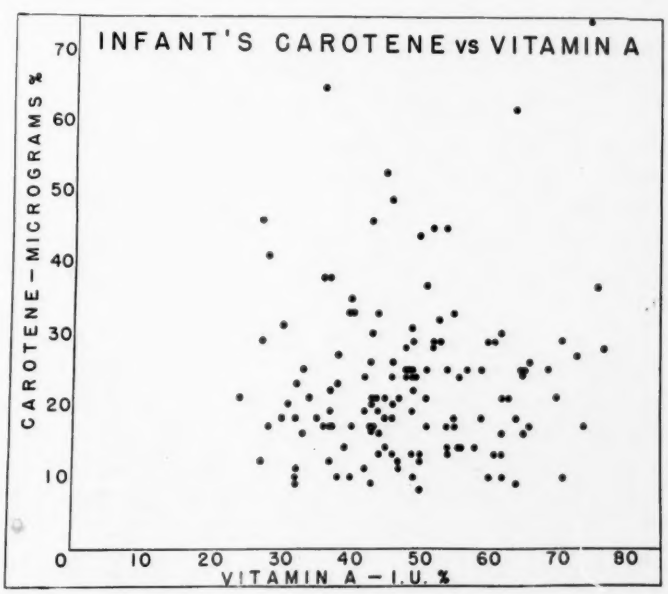

Fig. 6.—Showing infants' carotene values vs. plasma vitamin A values. There is no evidence of correlation.

of vitamin A in the fetal circulation is independent of the amount in the maternal circulation. The independence of the fetus in this respect was demonstrated in several ways:

First, there was inversion of the usual maternal-fetal relationship. Obviously inversion cannot occur until the maternal range of values has dropped below the level of highest fetal values. Inversion was limited to the range of subnormal maternal values and was manifested by the appearance of fetal values which sometimes equalled or exceeded those of the mother. It is probably fortuitous that inversion in the maternal-fetal relationship and subnormal adult values appeared simultaneously at maternal levels below 75 to 80 I.U. per cent. The frequency of inversion increased as maternal values decreased, a conclusion well illustrated by our data from the ten women with lowest values; eight of these women had inverted values. What the status of the maternal-fetal relationship would be under conditions of extreme maternal deficiency is a matter for interesting speculation. If the maternal level of vitamin A dropped below 24 I.U. per 100 ml., the lowest fetal value recorded by us, would all fetal values be higher? Speculation aside, our data demonstrated that the plasma vitamin A values of the infant are independent of the maternal values when the latter are in the range of deficiency.

The fetal values are equally independent of those of the mother under conditions of excessive vitamin A intake. Both moderate and large doses of vitamin A elevated the maternal blood plasma vitamin A to high levels, yet the fetal plasma vitamin A was not influenced.

Additional evidence of fetal independence was disclosed by the study of twin pregnancies, where wide variations were unexpected and unexplained. Boyd,[21] however, has noted similar wide variations in blood lipids of twins and we have also noted such variations in carotene and vitamin C. We are left with the unsatisfactory answer that such variations are inherent to the fetus as twin infants certainly have an identical maternal source of supply and the same placental barrier. These variations are probably associated with the distribution and utilization of supplies offered, and attention is called to the marked variation in weights of identical twins as another example of such a condition.

We therefore conclude that the fetus and mother are never in equilibrium as regards plasma vitamin A, excepting by chance. Furthermore, our evidence suggests that there may be little or no transmission of vitamin A through the placenta in either direction. If there is placental transmission it is not related to the amounts of vitamin A circulating in the maternal blood, but must be determined or limited by some intrinsic fetal factors.

The weight of the newborn infant is one factor associated with the plasma vitamin A of the cord blood; weight is also associated with deposition of fats which takes place late in gestation.[22] Our data

indicated a significant relationship between weight and vitamin A in infants below normal weight. Is it possible that this relationship may be associated with metabolism of fats? Boyd[21] has studied the placental transmission of three general groups of fats: (1) the phospolipids, which apparently pass the placental barrier with ease and are utilized by the infant in rather large amounts; (2) the cholesterols, which are present in smaller amounts and are apparently not so readily transmitted or utilized; and (3) the neutral fats, which sometimes pass the placental barrier, but may be synthesized by the fetus. Lasch[23] reported that vitamin A was associated with cholesterol and neutral fat, and recent investigators including Josephs[24] are of the opinion that both vitamin A and carotene, being fat soluble, are closely concerned with lipid chemistry. The type and amount of lipid with which vitamin A is associated and the ease or difficulty with which this combination of lipid and vitamin pass the placental barrier may be a determining factor in the fetal concentration of vitamin A. Further investigations along these lines are clearly indicated.

Straumfjord[25] suggested that the formation of vernix caseosa might be a manifestation of vitamin A deficiency. By prolonged administration of large doses of the vitamin to the mother he was able to reduce the frequent appearance of vernix caseosa in newborn infants. No blood determinations of vitamin A were made. In our series, which included blood determinations, we were unable to obtain any evidence of correlation between the plasma vitamin A of the fetus or its mother and the amount of vernix caseosa, even when the maternal values suggested moderate deficiencies.

No interpretation is offered for the fact that one infant with erythroblastosis and congenital anemia had by far the highest vitamin A value recorded for fetal plasma in our study.

Carotene.—The carotene concentrations in blood of the newborn infant are very low and are always much less than those of the mother. Yet in spite of this disparity, there is a definite relationship between the fetal and maternal values throughout the entire range of values. Fetal plasma concentrations were approximately one-tenth as high as maternal concentrations when the latter were average, one-eighth when the mothers' were low, and one-twelfth when the mothers' were high. This intimate relationship suggests a small but regular transfer of carotene from the mother to the fetus, and is in distinct contrast to independence of the mother and fetus as regards plasma vitamin A. We have no evidence to explain the physiologic differences of transmission of these two substances through the placenta, but we believe that differences in lipid solubility may be one of the important factors.

If the fetus does not receive vitamin A from the mother, there is but one other logical source: synthesis from carotene. The small but regular transfer of carotene from mother to fetus suggests this possibility. Yet the relationship can be traced no further as there is no

apparent correlation between the levels of carotene, either fetal or maternal, and fetal plasma vitamin A. This failure to show correlation does not necessarily invalidate the above suggestion for we know that the normal adult synthesizes vitamin A from carotene and still there is no demonstrable correlation between plasma carotene and plasma vitamin A.[13]

Two aspects of this research concerning vitamin A are significant clinically: one is the apparent independence of the fetus as regards plasma concentrations of the vitamin; the other is the comparatively small amounts of vitamin A found in the plasma of the newborn infant.

It has long been said that the fetus lives as a parasite upon its mother and adequate fetal nutrition is usually maintained in the presence of maternal starvation. Our data suggest a similar relationship for vitamin A because the fetus maintained values for the vitamin within a moderate range regardless of mild or moderate maternal deficiencies. In such degrees of deficiency we need not concern ourselves with the state of the fetus for as far as the *fetus* is concerned there would seem to be no advantage in giving the mother excessive amounts of vitamin A, for we were unable to elevate the fetal plasma vitamin A under such conditions.

The same statement does not obtain for carotene. Maternal carotene deficiencies are reflected by the fetus as are maternal carotene excesses, although concentrations in the fetal blood are always much less than those of the mother. Although our knowledge of carotene metabolism is incomplete we can say that the fetus is dependent on the mother for an adequate amount of carotene which can be supplied by a diet adequate in yellow and green leafy vegetables.

The infant is born with a small complement of vitamin A and should be assured of an adequate intake during early prenatal life. This is particularly true of infants of subnormal weight. Under ordinary conditions the only source of vitamin A during the first few weeks of life is human or cow's milk. Human colostrum and early breast milk contain adequate amounts of vitamin A and constitute the ideal source of supply. Cow's milk, which contains smaller amounts of vitamin A, is often used as a substitute for the human product. Such substitution is undesirable during the first two weeks of life but if it is absolutely necessary the addition of vitamin A to the cow's milk is clearly indicated.

Summary and Conclusions

1. The values obtained by a reliable method of chemical analysis for plasma vitamin A of normal newborn infants were approximately one-half as high as normal adult values.

2. Plasma vitamin A of the newborn infant was independent of maternal plasma vitamin A regardless of the mother's intake of this vitamin. Low maternal values were not reflected by the fetus, and in many such instances the fetal values were similar or higher. Adminis-

tration of excessive amounts of vitamin A to the mother elevated the maternal blood values but was without effect on the fetal blood values.

3. Plasma vitamin A of infants below average weight was usually low, while that of infants above average weight varied within the normal range for infants.

4. Plasma carotene from the umbilical cord of newborn infants was approximately one-tenth as high as maternal plasma carotene when the latter were average, one-eighth when the maternal values were low, and one-twelfth when they were high.

5. Fetal plasma carotene varies regularly with maternal plasma carotene and can be estimated with considerable accuracy by a mathematical equation showing a curvilinear relation.

6. There was no correlation between fetal plasma carotene and vitamin A, yet this does not necessarily exclude carotene as a precursor of fetal vitamin A.

7. Vitamin A, in contrast to carotene, either is not transmitted or is poorly transmitted from the mother to the fetus. In this respect it resembles certain lipids, and vitamin A transmission through the placenta may be related to or limited by lipid metabolism at the placental barrier.

8. The newborn infant should be assured of an adequate supply of vitamin A during early life. Human colostrum and early breast milk are the ideal source of supply, but if cow's milk is substituted there is need for additional vitamin A.

References

1. Wendt, H.: Klin. Wchnschr. **15**: 222, 1936.
2. Dann, W. J.: Biochem. J. **26**: 1072, 1932.
3. Dann, W. J.: Biochem. J. **28**: 634, 1934.
4. Ellison, J. B., and Moore, Thomas: J. Soc. Chem. Ind. **55**: 236, 1936.
5. Neuweiler, W.: Klin. Wchnschr. **14**: 1040, 1935.
6. Neuweiler, W.: Arch. Gynäk. **162**: 384, 1936.
7. Gaehtgens, G.: Klin. Wchnschr. **16**: 893, 1937.
8. Gaehtgens, G.: Ibid. **16**: 894, 1937.
9. Gaehtgens, G.: Ibid. **16**: 1073, 1937.
10. Gaehtgens, G.: Ibid. **16**: 1075, 1937.
11. Clausen, S. W., and McCoord, A. B.: J. Pediat. **13**: 635, 1938.
12. Toverud, K. V., and Ender, F.: Acta. Paed. **18**: 174, 1938.
13. Kimble, M. S.: J. Lab. & Clin. Med. **24**: 1055, 1939.
14. Dann, W. J., and Evelyn, K. A.: Biochem. J. **32**: 1008, 1938.
15. May, C. D.: Program Amer. Instit. of Nutr., Meeting, Baltimore, 1939.
16. Barbour, J. H.: Unpublished data.
17. Murrill, W. A., Horton, P. B., Leiberman, E., and Newburg, L. J.: J. Clin. Investigation **20**: 395, 1941.
18. Blaisdell, J. L.: Personal communication to one of us (M. S. K.), 1942.
19. Scalonge, H. W.: Acta. brev. Neerland. **10**: 181, 1940.
20. Getz, H. R., and Koerner, T. A.: Am. J. M. Sc. **202**: 831, 1941.
21. Boyd, Eldon M., and Wilson, Karl M.: J. Clin. Investigation **14**: 7, 1935.
22. Hugget, A. St. G.: Physiol. Rev. **21**: 438, 1941.
23. Lasch, F.: Klin. Wchnschr. **13**: 1534, 1934.
24. Josephs, Hugh W.: Bull. Johns Hopkins Hosp. **71**: 625, 1942.
25. Straumfjord, John V.: West. J. Surg. Obst. & Gynec. **48**: 341, 1940.

THE ACTION OF SYNTROPAN ON THE UTERUS*

J. A. Wells, Ph.D., D. D. Albers, M.S., and A. C. Ivy, Ph.D., M.D.
Chicago, Ill.

(From the Departments of Pharmacology and Physiology, Northwestern University Medical School)

IT HAS been reported that syntropan (the phosphate of the dl-tropic acid ester of 3-diethylamino-2, 2-dimethyl-1-propanol) hastens the first stage of labor in the human being.[1-6] This drug is claimed to effect an increase in the rate of dilatation of the cervix and it is implied that the principal mechanism is one of accelerated cervical relaxation.

Studies of the action of syntropan on experimental animals have revealed that this drug causes contraction of the intact uteri of nonpregnant and pregnant rabbits.[7] It has also been shown that syntropan causes contraction of uterine strips from nonpregnant rabbits; nonpregnant guinea pigs; nonpregnant cats (pregnant cat uteri were relaxed by syntropan); and nonpregnant human beings.[7, 8, 9]

The purpose of the present investigation was (1) to confirm and extend certain of the existing information on the action of syntropan on the excised uterine strip; (2) to study the action of syntropan on the intact animal uterus; and (3) to obtain information on the action of syntropan on the intact, unanesthetized, pregnant animal prior to spontaneous delivery.

Method

The action of syntropan** on the uterine strip has been studied in nonpregnant, pregnant, and post-partum rats; nonpregnant, pregnant, post-partum, and progesterone treated nonpregnant guinea pigs; and pregnant human beings. The progesterone treated strips were obtained from non-pregnant guinea pigs which were injected subcutaneously with 5.0 mg. of progesterone in oil† daily for five days. These uteri were studied on the eighth day, and at this time showed marked endometrial growth. The human uterine strips were obtained at the time of elective cesarean section in patients who were not in labor.‡

Strips of the various uteri were suspended in a small bath (7.5 c.c.) containing a modified Sollmann-Rademaekers solution (NaCl 9.0 Gm./L.; $CaCl_2$ 0.12 Gm./L.; KCl 0.423 Gm./L.; $NaHCO_3$ 0.32 Gm./L.; and dextrose 0.5 Gm./L.). The bath was maintained at 38° C., and the solution was constantly aerated.

The syntropan was made up to 1 per cent strength in portions of the above solution, and was kept at the same temperature as the bath.

*Assisted in part by a grant from Hoffmann-La Roche, Inc.

**Furnished to us by Hoffmann-La Roche, Inc., through the courtesy of Mr. E. W. Marti and Mr. W. P. Freeman.

†Furnished to us by Roche-Organon, Inc., through the courtesy of Mr. E. W. Marti and Mr. W. P. Freeman.

‡Furnished to us through the courtesy of Dr. B. Mortimer.

In most instances enough of this 1 per cent syntropan was added to the bath to make the final concentration 1:3,000.

Studies have been carried out on the change of pH of the bath as produced by syntropan. A glass electrode pH meter was employed. In the control procedure, in which the pH was altered by the same amount as by syntropan, dilute hydrochloric acid was employed.

Studies of the action of syntropan on intact post-partum uteri have been performed on immediately post-partum (within 48 hours) guinea pigs and dogs. Sodium pentobarbital anesthesia was employed, and the activity of the uteri was recorded by means of balloon water manometer systems.

In the guinea pigs the balloon was introduced into the uterus by way of the vagina. In the dogs the abdomen was opened and one balloon was introduced into the body of the uterus by way of a small incision in the wall of the uterus, and another balloon was placed in the cervix. This latter balloon was of a cylindrical type with rigid metal ends so arranged that only a circular type of movement was recorded.

Injections of syntropan (2 to 20 mg./kg.) were made intravenously; via the jugular vein in the guinea pig, and via the femoral vein in the dog.

Studies of the action of syntropan on pregnant unanesthetized animals were performed on guinea pigs and rats. Dated pregnancies were obtained by the following techniques. It is well known that the rat and the guinea pig exhibit a more or less uniform estrus cycle. The period of estrus in the guinea pig is grossly characterized by solution of a membrane which at all other times seals the vagina. Therefore, dated pregnancies were obtained in guinea pigs by the simple procedure of placing males with females for only one of these periods when the vagina was open. In our colony of guinea pigs the duration of vaginal canalization was approximately three days. Therefore, if it is assumed that fertilization occurred on the middle day of vaginal opening, then the recorded duration of gestation can be in error by only plus or minus half of the period of vaginal opening in any given animal.

In the rat the technique of obtaining dated pregnancies was one of repeated breeding of the colony at two-day intervals. Feti are readily palpable on the fourteenth but not on the twelfth day of gestation. Therefore, it is felt that by this technique the duration of gestation can be determined with an accuracy of one day.

Normal gestation periods were determined in a series of rats and guinea pigs, and using these average values for reference standards treatment was carried out in other series of animals at uniform intervals prior to spontaneous delivery. In general, treatment was begun in the guinea pigs six days, and in the rats four days before the calculated delivery date.

In the guinea pig it is known that there is a marked separation of the symphysis pubis which occurs from one to several days prior to spontaneous delivery.[10, 11] As an additional check, careful palpation of the treated animals in the present study revealed that no such separation had occurred at the time of treatment.

Treatment of the guinea pigs consisted of the intraperitoneal injection of 1 c.c. of a 1 per cent syntropan solution every half-hour for a series of ten injections, or a total dose of 100 mg. In a second series of animals comparable subcutaneous injections of syntropan were per-

formed. In a control series of animals 0.9 per cent sodium chloride rather than syntropan was injected intraperitoneally. Treatment of the rats consisted of a series of eight half-hourly intraperitoneal injections of 1 c.c. of 1 per cent syntropan solution.

All injected animals were observed for a period of 24 hours from the beginning of the injections and deliveries were recorded as those which occurred within the 4.5-hour treatment period and those which occurred during the subsequent 19.5 hours. Any deliveries which occurred more than 24 hours from the time of injection were disregarded because of the encroachment in time upon the range of observed spontaneous deliveries in the control series of animals. However, in the control series no animals had spontaneously delivered by this time.

Results

Studies of the In Vitro Action of Syntropan.—Syntropan in a concentration of 1:3,000 produced a variable response of the uterine strips. In each instance either contraction or relaxation of the strip in response to this drug was observed, but the direction of the response was constant for any given strip.

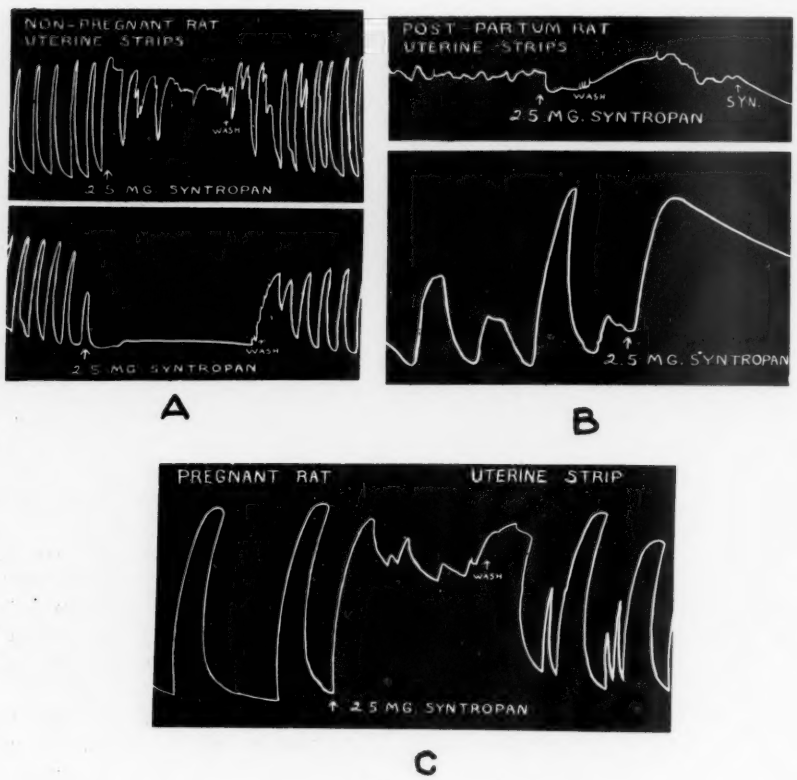

Fig. 1.

Relaxation in the present studies implies either an elimination of spontaneous contraction with a progressive loss of tone, or in certain instances, simply a cessation of spontaneous activity. In all cases spontaneous activity returned when the syntropan was washed from

the bath. Contraction implies either a single prolonged contraction with tone remaining above the basal level or an increase in frequency of contraction with an elevation of tone.

Rats.—It can be seen (Table I) that in a series of uterine strips from 9 nonpregnant rats, 4 were relaxed and 5 were contracted by syntropan (Fig. 1-*A*). Uterine strips from 10 pregnant rats were all contracted by syntropan (Fig. 1-*C*). In a series of 6 uterine strips from post-partum rats (1 to 1.5 days), 3 were relaxed and 3 were contracted by syntropan (Fig. 1-*B*).

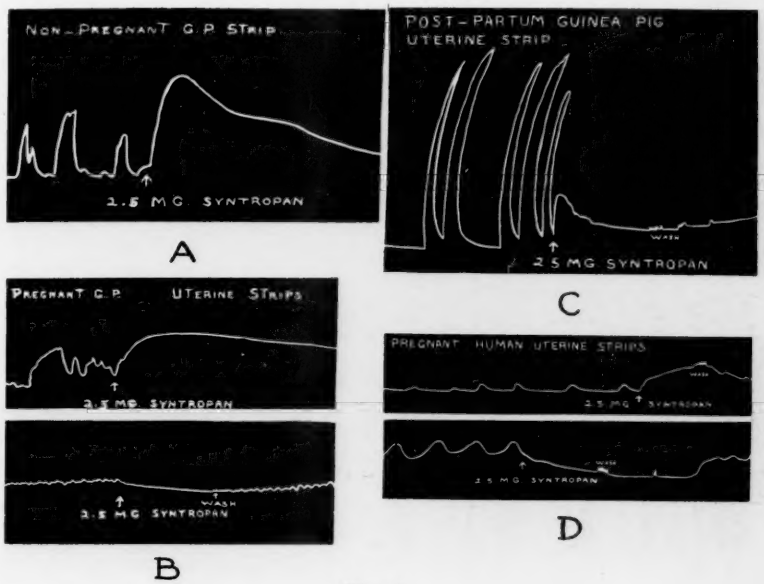

Fig. 2.

TABLE I. ACTION OF SYNTROPAN ON EXCISED UTERINE STRIPS

TYPE OF ANIMAL	TYPE OF UTERUS	NO. OF ANIMALS	RESPONSE	
			RELAXATION	CONTRACTION
Rat	Nonpregnant	9	4	5
	Pregnant	10	0	10
	Post-Partum	6	3	3
Guinea pig	Nonpregnant	10	0	10
	Pregnant	10	3	7
	Post-Partum	11	9	2
	Progesterone Treated Nonpregnant	7	0	7
Human	Pregnant	9	4	5

Guinea Pigs.—In the guinea pig (Table I) a series of uterine strips from 10 nonpregnant animals were all contracted by syntropan (Fig. 2-*A*). In a series of uterine strips from 10 pregnant animals, 3 were relaxed and 7 were contracted by syntropan (Fig. 2-*B*). In a series of uterine strips from 11 post-partum guinea pigs, 9 were relaxed (Fig. 2-*C*) and 2 were contracted by syntropan.

An attempt was made in a series of seven nonpregnant guinea pigs to determine whether the response of the isolated uterus to syntropan could be altered by the administration of progesterone. However, even

though large doses of this drug were used the response of these uteri remained typical of the nonpregnant animal, and all strips were contracted by syntropan (Table I).

The addition of syntropan to the muscle bath in a final concentration of 1:3,000 lowered the pH of the bath from 7.9 to 7.0 at the time the response of the muscle occurred. Similar depression of the pH by HCl did not produce the characteristic response of the uterine strip (Fig. 3-*C*).

Human Beings.—In a series of nine uterine strips obtained from patients by cesarean section (Table I) four were relaxed and five were contracted by syntropan (Fig. 2-*D*).

Studies of the action of syntropan upon the post-partum uterus in situ have revealed that in a series of 10 guinea pigs the intravenous injection of syntropan (10 to 20 mg./kg.) caused an immediate increase in the intrauterine pressure (Fig. 3-*A*). This response was not produced by the control injection of saline. The duration of this response varied from 2 min., 38 sec. to 17 min., 7 sec. with an average of a little over 9 min. A similar response could be elicited by a subsequent injection of the same amount of drug.

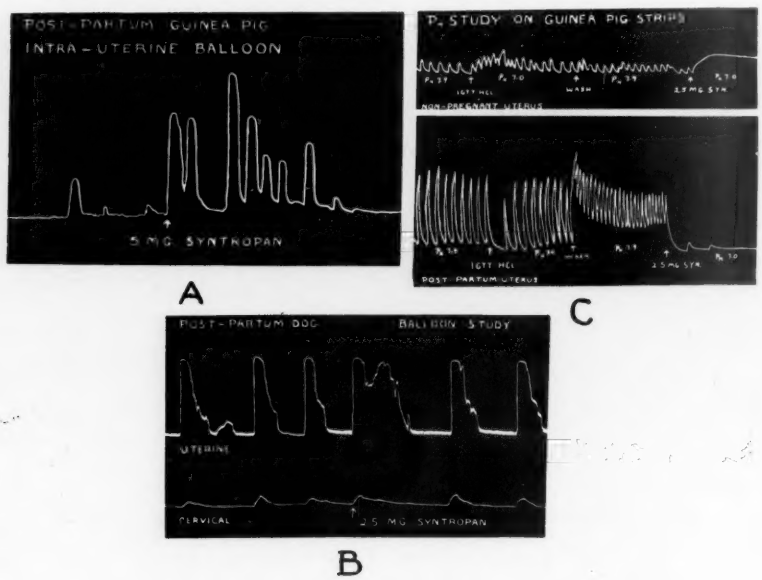

Fig. 3.

In a series of 5 post-partum dogs the intravenous injection of syntropan (2 to 8 mg./kg.) caused an immediate contraction of the uterus (Fig. 3-*B*). This response was marked but brief, lasting only 3 to 5 min. In these same animals a balloon was placed in the cervix, and while it is difficult to ascertain whether increased cervical contractions occurred, it is very evident that cervical relaxation in response to syntropan definitely did not occur.

Studies of the action of syntropan on the intact pregnant animal required a preliminary determination of the normal gestation period. A study of 18 normal guinea pigs revealed that the average day of

delivery was 66.1 ± 3.42* days from the assumed day of fertilization. None of these animals delivered before the sixty-second day. In a similar series of normal rats the average delivery date was 22.0 ± 0.7 days from the assumed day of fertilization.

It can be seen (Table II) that in a series of seventeen guinea pigs injected intraperitoneally with saline 59.6 ± 3.0 days after the assumed day of fertilization, no animals delivered within the 4.5-hour treatment period. However, eleven or 64.7 per cent of these animals delivered within the next 19.5-hour period. In a comparable series of thirty-three guinea pigs injected intraperitoneally with a total of 100 mg. of syntropan 58.4 ± 2.15 days after the assumed day of fertilization, sixteen or 48.5 per cent delivered within the 4.5-hour treatment period. Seven animals or 21.2 per cent delivered during the ensuing 19.5 hours, making a total of 69.7 per cent delivering within the 24-hour period.

TABLE II. ACTION OF SYNTROPAN ON THE PREGNANT ANIMAL

TYPE OF ANIMAL	SERIES	NO. OF ANIMALS	AVG. DURATION OF GESTATION AT TIME OF TREATMENT (DAYS)	ROUTE OF INJECTION	ANIMALS DELIVERING					
					WITHIN 4.5 HOURS		WITHIN NEXT 19.5 HOURS		TOTAL	
					NO.	%	NO.	%	NO.	%
Guinea pig	Untreated controls	18	60.0*	--	0	0	0	0	0	0
	Saline controls	17	59.6 ± 3.0	Intraperitoneal	0	0	11	64.7	11	64.7
	Syntropan	33	58.4 ± 2.15	Intraperitoneal	16	48.5	7	21.2	23	69.7
	Syntropan	12	59.8 ± 2.28	Subcutaneous	1	8.3	2	16.7	3	25.0
Rat	Untreated controls	20	18.0†	--	0	0	0	0	0	0
	Syntropan	12	18.0 ± 0.84	Intraperitoneal	0	0	2	16.7	2	16.7

*Avg. Gestation Period = 66.1 ± 3.42 days.
†Avg. Gestation Period = 22.0 ± 0.7 days.

In a series of twelve guinea pigs injected subcutaneously with a total of 100 mg. of syntropan 59.8 ± 2.28 days after the assumed day of fertilization, 1 animal delivered during the ensuing 19.5 hours, making a total of 25 per cent delivering during the 24-hour period following the beginning of injection.

In a series of twelve pregnant rats which were injected intraperitoneally with a total of 80 mg. of syntropan (Table II), no animals delivered within the treatment period. However, two animals, or 16.7 per cent, delivered within the following 19.5 hours.

Discussion

The present findings are in agreement with those of others who claim that syntropan causes contraction of the nonpregnant guinea pig uterus in vitro.[8, 9] Contraction in response to syntropan was also uniformly obtained with pregnant rat uterine strips. However, the possibility that this drug could cause either contraction or relaxation

*The standard deviation of the distribution was calculated by the formula:

$$\sigma \sqrt{\frac{\Sigma X^2}{N} - Mx^2}$$

of the other types of uterine strips tested has not heretofore been mentioned. The mechanism by which a drug can produce opposite phenomena in one and the same type of uterine strip is not at the present time explainable, but a similar situation is known to exist in the case of the action of epinephrine on the uterine strip.[12]

The suggestion has been made that syntropan produces a response of the isolated muscle because it lowers the pH of the bath.[9] The present observations indicate that syntropan is capable of lowering the pH of the bath at the time that the characteristic response of the muscle occurs. However, while an equal lowering of the pH by the addition of a small amount of acid is associated with a slight change in the activity of the muscle, it by no means produces the characteristic muscular response of the drug.

Whatever the final interpretation may be, the evidence indicates that syntropan has an action on the isolated uterine strip. Such evidence would suggest that syntropan may produce its effect in the animal by direct muscular action rather than by blocking a cholinergic mechanism.

It is known that experimental alteration of the hormone level of certain animals will change the response of the uterine strip to certain drugs acting on the uterus.[13, 14] However, the present inability to alter the response of the nonpregnant guinea pig uterus to syntropan by pretreatment of the animal with progesterone is in agreement with similar observations on the rabbit.[7]

The implication found in the clinical literature that syntropan hastens cervical dilatation by relaxing the cervix does not receive support from the present observation that this drug does not relax the cervix of the post-partum dog. While there is no reason to assume that the two situations are in any way comparable, there is also no reason to assume that an increased rate of cervical dilatation can be accomplished only by a specific relaxation of the cervix. In all probability cervical dilatation is a physiologic adjustment to the presenting part and is accomplished by effective contractions of the body of the uterus. Therefore, it would appear that hastening of cervical dilatation might best be accomplished by a drug which increased the effectiveness of the contractions of the body of the uterus.

The present observations that a small per cent of guinea pigs delivered offspring following the subcutaneous injection of syntropan, coupled with the fact that a substantial number of animals delivered during a series of intraperitoneal injections of this drug, might seem to indicate that this drug is capable of inducing labor before normal term in these animals. However, the finding that a similar substantial number of animals delivered following the intraperitoneal injection of saline, but after a longer time interval, would seem to indicate that syntropan acts to speed materially the nonspecific induction of labor produced by repeated intraperitoneal injection of the guinea pig.

Summary and Conclusions

1. Uterine strips respond to the administration of a 1:3,000 dilution of syntropan. Contraction in response to syntropan occurs in nonpregnant guinea pig and pregnant rat uterine strips. Either contraction or relaxation in response to syntropan occurs in nonpregnant and post-partum rat; pregnant and post-partum guinea pig; and pregnant human uterine strips. Such evidence would suggest a direct muscular action of this drug in the animal.

2. The slight alteration of the pH of the muscle bath produced by the addition of syntropan is not responsible for the characteristic action of this drug on the uterine strip.

3. Progesterone treatment of the nonpregnant guinea pig does not alter the response of a strip of its uterus to syntropan.

4. The intravenous injection of syntropan causes a temporary increase in the contractions of intact post-partum guinea pig and dog uteri. The cervix of the post-partum dog uterus is not relaxed by syntropan.

5. Syntropan in suitable concentrations significantly accelerates the nonspecific induction of labor produced by repeated intraperitoneal injection of the pregnant guinea pig. However, a similar phenomenon does not occur to any significant degree in the pregnant rat.

References

1. Psychyrembal, W.: Med. Klin. **48**: 1599, 1934.
2. Gamstaetter, H.: München. med. Wchnschr. **82**: 1491, 1935.
3. Hirsch, F. E.: Brit. M. J. **2**: 559, 1937.
4. Peine, E.: Therap. d. Gegenw. **7**: 333, 1935.
5. Stoll, J. E.: Am. J. Obst. & Gynec. **42**: 473, 1941.
6. Hillis, D. S., and Beaton, J. H.: Unpublished observations.
7. Clark, B. B., and Shires, E. B. S., Jr.: J. Pharmacol. and Exper. Therap. **70**: 378, 1940.
8. Samann, K., and El Asreegy, M. I.: Quart. J. Pharm. and Pharmacol. **8**: 186, 1935.
9. Fromherz, K.: Quart. J. Pharm. and Pharmacol. **9**: 1, 1936.
10. Todd, T. W.: Am. J. Anat. **31**: 345, 1923.
11. Hisaw, F. L.: Proc. Soc. Exper. Biol. & Med. **23**: 661, 1926.
12. Miller, E. G., Cockrill, J. R., and Kurzrok, R.: Am. J. Obst. & Gynec. **33**: 154, 1937.
13. Robson, J. M.: Quart. J. Exper. Physiol. **22**: 7, 1932.
14. Van Dyke, H. B., and Gustavson, R. G.: J. Pharmacol. and Exper. Therap. **37**: 379, 1929.

A TWENTY-SIX-DAY HUMAN EMBRYO*

WILLIAM E. STUDDIFORD, M.D., NEW YORK, N. Y.

(From the Obstetrical and Gynecological Service [III Division] Bellevue Hospital, and from the Department of Obstetrics and Gynecology, New York University College of Medicine.)

IN RECENT years there has been a reawakening of interest in the early stages of human embryology. While we were formerly dependent for our knowledge on the accidental discovery of a small number of human specimens, few of which were perfect, and many of which were incomplete or defective, recent well-planned search has resulted in the description of a relatively large series of fertilized ova, the youngest of which is beginning the process of nidation. Renewed interest in this important subject can be attributed largely to the efforts of Rock and Hertig[1] in cooperation with the Department of Embryology of the Carnegie Institution of Washington.[2] These workers have discovered and described twelve early human ova varying in age from 7½ to 16 days, and moreover in each instance, have supplied the data dealing with the clinical background relating to each specimen. This study has cast important light on the time of ovulation and fertilization and has demonstrated that, occasionally, visible uterine bleeding of variable quantity and duration may accompany the process of nidation.

The specimen which is to be presented is quite elderly in comparison to those of Rock and Hertig. Nevertheless it is of interest because it has been pronounced perfect and because it casts some light on the causation of uterine bleeding occurring in the early months of pregnancies which otherwise pursue a normal course.

Before presenting this specimen a few words should be said as to the manner in which it was obtained.

Mrs. M. C., 37 years old, para vii, gravida viii, was admitted as an emergency case to the obstetric service of Bellevue Hospital on Jan. 7, 1941, in the eighth month of pregnancy, complaining of headache and loss of vision. On examination she showed marked generalized edema, a blood pressure of 235/130, and a hemorrhagic retinitis. Her urine boiled solid with albumin. After a short period of observation, labor was induced by rupture of the membranes through a partially dilated, soft, thin cervix, and by the administration of pituitrin. After a short labor, she was delivered of a normal 5½ pound premature infant which survived. Following delivery, gradual improvement took place in the mother, the retinitis clearing up, but a moderate degree of hypertension and albuminuria persisting up to the time of discharge.

*Presented at a meeting of the New York Obstetrical Society, March 9, 1943.

Post-partum sterilization was considered but the idea was abandoned because of the somewhat precarious condition of the patient. Because she had five living children and had shown evidence of toxemia in some of her other pregnancies, she was given contraceptive advice, strongly warned against the danger of any further pregnancies, and was requested to report to the hospital at once if ever she suspected herself to be pregnant.

Recalling the latter advice, she returned to the hospital on Sept. 23, 1942, stating that her last menses had occurred on August 18, and that she believed herself to be pregnant. Although she appeared older than her stated age, her general physical examination was negative except for a few findings. Her blood pressure, which had been found to be 210/130 before admission, dropped to 140/100 after twenty-four hours' rest in bed. On bimanual examination the uterus felt soft and a little enlarged. The urine showed a trace of albumin. After discussing the situation with the patient, she agreed to the removal of her uterus as the most certain method of terminating the present pregnancy and preventing a recurrence of this situation. Accordingly on Sept. 25, 1942, thirty-eight days after the last menses, a high supravaginal hysterectomy was performed, leaving a small part of the lower corpus so that menstruation would continue. Her postoperative course was uneventful and she was discharged on October 8, 1942.

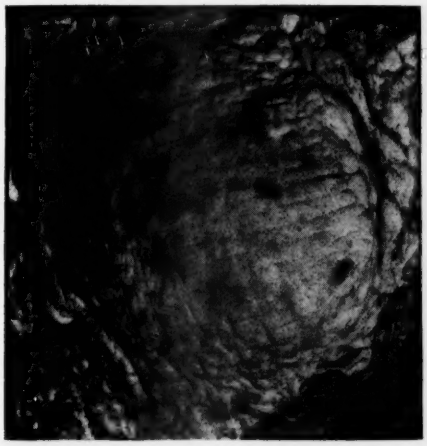

Fig. 1.—Nidation site (×2). The smooth mound, under which lies the ovum, measured 2 cm. in diameter. The surrounding decidua vera shows an uneven surface marked by furrows and crypts. The point at which it joins the decidua capularis is marked by a sulcus which almost surrounds the nidation site. Note areas of discoloration in decidua capsularis. Regular network of lines on decidua capularis is due to gauze being laid over fresh specimen during process of fixation.

The specimen was examined immediately on removal and consisted of the upper ¾ of the uterine corpus. It appeared slightly bluish in color, a little enlarged and softened in consistency. The uterus was opened by the method advised by Hertig in order to avoid injury to the contained ovum, an incision being made through the depth of the myometrium along the left border of the organ to the left cornua and across the fundus to the right cornua. The incision was completed by dividing the decidua with a pair of fine scissors. The uterus was then laid open much as one would open a book. The myometrium appeared to be slightly increased in thickness and the cavity was lined with a

pale mucous membrane 8 to 9 mm. in thickness, the surface of which was made irregular by low polypoid projections separated by crevices and furrows. The ovum was easily detected on the middle of the posterior wall to the left of the midline. Here was noted a low mound about 2 cm. in diameter projecting slightly above the surrounding decidua. The central portion of this structure showed a smooth, semi-translucent surface and was bluish in color. The borders were indistinct, merging gradually with the surrounding decidua vera, the beginning of which was marked by a crevice which seemed to encircle the nidation site. The specimen was placed immediately in Bouen's solution and allowed to fix for twenty-four hours. At the end of this time, a square block was excised from the uterine wall including the nidation site and the surrounding decidua vera (Fig. 1). The outer layers of the myometrium were cut away and the specimen was allowed to fix for twenty-four hours more. It was then placed in 80 per cent alcohol and sent to the Department of Embryology of the Carnegie Institution of Washington. Through the kindness of George W. Corner, this specimen was placed in the hands of Chester Heuser for detailed study. The following is based on his report.

Fig. 2.—A portion of the amnion has been removed disclosing the embryo which measured 5.3 mm. in length. The large round structure adjacent to the amnion is the yolk sac. (×8.)

The ovum, submerged in 80 per cent alcohol, was dissected under the binocular microscope. At various steps during the progress of the work, stereophotographs were taken in order to preserve an adequate record of the relationships. A small piece of the decidua capsularis with the underlying chorionic wall was first excised in order to determine the position of the embryo. The extra-embryonic space within the chorionic plate was found to be filled with rather dense coagulum. Some of this material was carefully removed, bringing into view the yolk sac. The embryo, enclosed in the slightly expanded amnion, was next found attached to the usual site; that is, to the deep part of the inner aspect of the chorionic plate. Due to precipitation

of the proteins on the external surface of the amnion, the body of the embryo could be seen only faintly. It seemed best, therefore, to dissect off enough of the amnion to expose the body stalk (Fig. 2). The latter structure was then cut across close to the chorionic wall and the embryo and yolk sac were removed. The embryo appeared entirely normal and symmetrical. It was strikingly similar to a monkey embryo of 26¾ days' fertilization age and measured 5.3 mm. in its maximum length. The arm buds were definite and the leg buds were just appearing (Fig. 3). The embryo was embedded by the double colloidin-paraffin method and has been sectioned at 6 microns by the water-on-the-knife procedure. These sections are at present being studied.

The empty chorionic sac with its surrounding decidua was returned to the pathologic laboratory at Bellevue Hospital where additional sections were prepared in order to study the relationship of the chorion to the decidua. The details of these sections are best shown by Figs. 4 to 9.

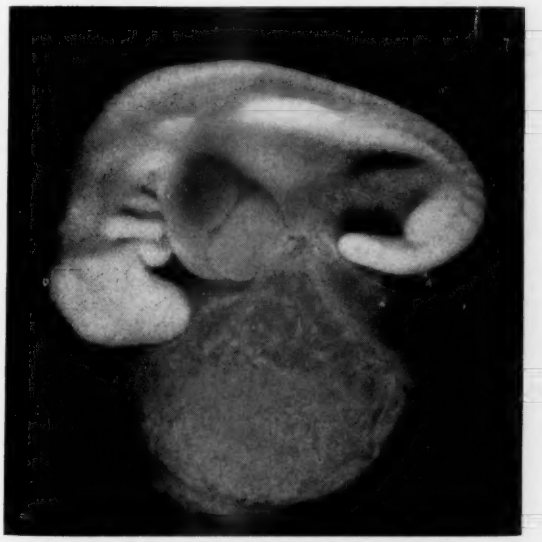

Fig. 3.—Embryo and yolk sac, lateral aspect. Note beginning limb buds. (×12.)

Discussion

Two points may be raised in the discussion of this specimen. The first has to do with the duration of the pregnancy. Dr. Heuser was able to state by comparison with a monkey embryo that the age was about 26½ days. Granted that this deduction was correct, the day of fertilization must have been August 31, the twelfth day after the beginning of the last menses. This date would coincide with the beginning of the portion of the menstrual cycle during which ovulation is believed to occur most commonly and when fertilization of the ovum is therefore most possible. His estimation of the age by comparison and the possible age as calculated from the menstrual history, therefore, are closely similar.

The second point of interest lies in the degenerative and hemorrhagic changes which have already taken place at this early stage of pregnancy in the decidua capsularis. These changes are limited to this area, no

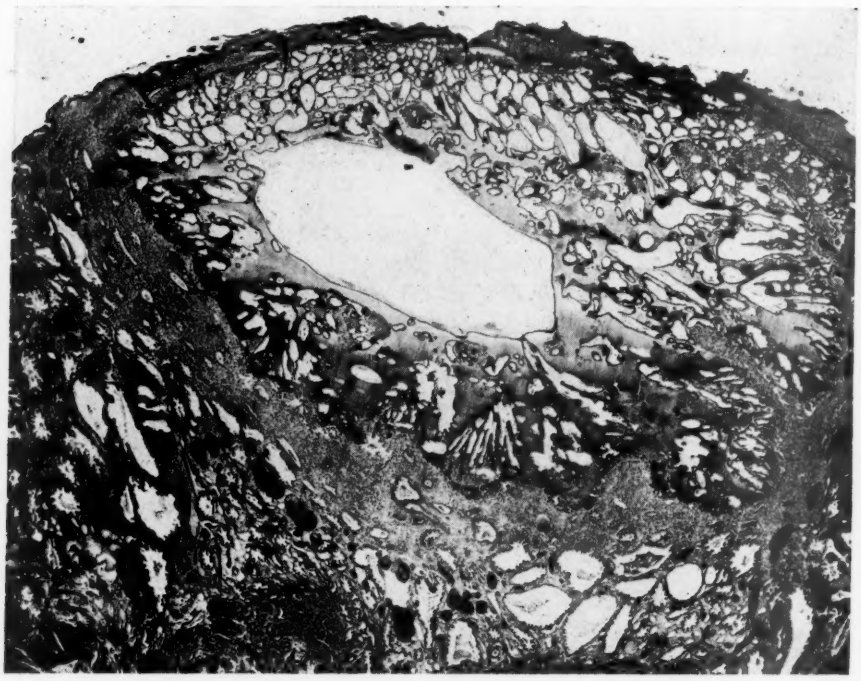

Fig. 4.—Low power microphotograph showing the empty chorionic vesicle (the embryo, amnion, and yolk sac having been removed), lying in the maternal blood space and surrounded by a mantle of decidua. Note the extreme thinning of the decidua capularis. The irregularity of the surface is due to artefact.

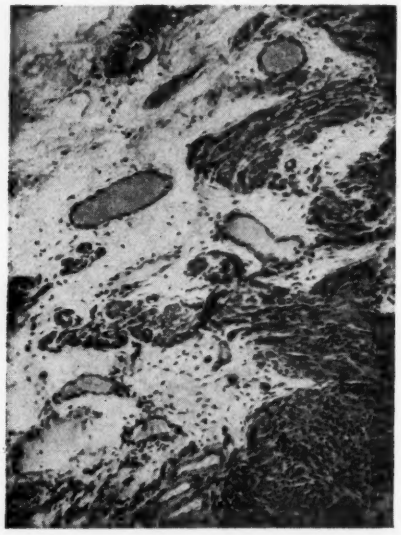

Fig. 5.—Edema of outer third of myometrium with dilatation of blood vessels. Hypertrophy of muscle cells has not as yet taken place. This change must account in part for the softening and enlargement of the uterus.

evidence of them being found in the decidua vera. It seems most likely that they are related to the stretching and distention of the thin layer of decidua separating the maternal blood space from the uterine cavity, rather than to any lack of progesterone stimulation.

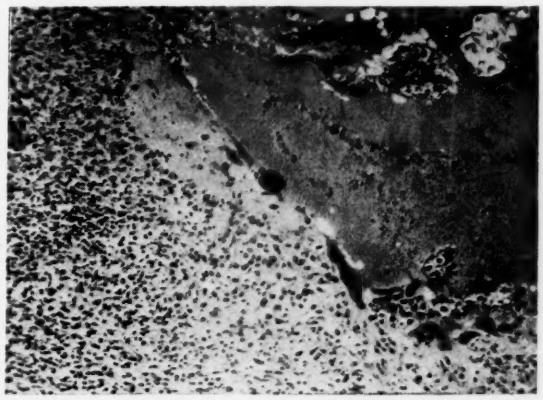

Fig. 6.—Lining of maternal blood space, showing partially broken down decidua and the beginning of a marginal layer of fibrinoid material, along the surface of which syncytial cells are arranging themselves.

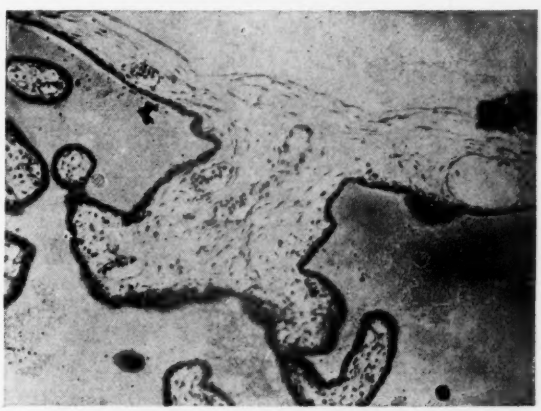

Fig. 7.—Stalk villus springing from chorionic plate and containing vessels filled with nucleated red blood cells.

Hertig and Rock have demonstrated that uterine bleeding, usually slight, but variable in quantity and duration, may announce the nidation of a uterine pregnancy. It is not difficult to imagine that these lesions may account for the bleeding which occurs not infrequently at a later period in the first trimester of pregnancies which otherwise pursue a normal course. Furthermore, it is easy to imagine the rupture of the superficial wall of the maternal blood space of an early pregnancy which is otherwise normal. Such a rupture will result in quite profuse fresh uterine hemorrhage and unless promptly sealed by thrombosis, will result in the loss of a normal pregnancy. With the presence of such lesions, trauma does not have to be considered as an additional factor. Uterine bleeding and abortions occurring in the first trimester accompanied by this characteristic bleeding may be said

to be caused by accidental hemorrhage of early pregnancy. It is particularly difficult to see what influence progesterone therapy would have on the course of this condition. The sudden bright bleeding characteristic of this type of abortion offers itself in sharp contrast to the gradual appearance of an increasing brownish uterine discharge which so often precedes the abortion of a defective ovum.

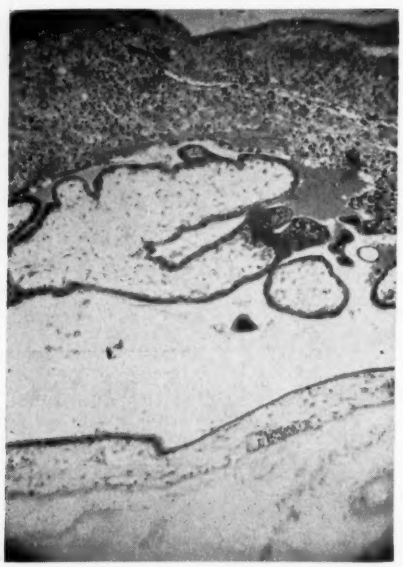

Fig. 8.—Higher magnification of decidua capularis, showing infiltrating hemorrhage and degeneration.

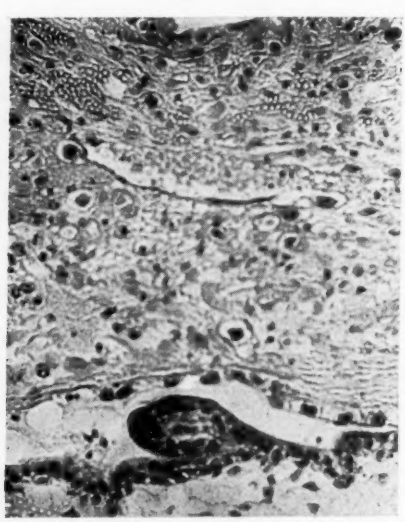

Fig. 9.—High power magnification of decidua capularis showing infiltrating hemorrhage.

References

1. Rock and Hertig: Am. J. Obst. & Gynec. 44: 973, 1942.
2. Hertig and Rock: Carnegie Institution of Washington Publication No. 525: 127-156, 1941.

Discussions

DR. DONAL SHEEHAN (by invitation).—A specimen like this is of enormous importance because we are too dependent in our teaching of embryology upon chick and pig embryos. Up until a short time ago there existed only a few human embryos for study. The Peters and the Teacher-Bryce embryos turned out in the light of recent work to be abnormal, and their ages as at first estimated are no longer accepted. The Miller and the Müller embryos are each represented by only few odd sections.

The early cleavage of the fertilized human ovum has never been seen, though we have learned a great deal about it from the monkey. At the Carnegie Institution, Dr. Streeter and his collaborators have made a careful study of the early cleavage in the monkey. During the first thirty days, the stages are presumably very close to those of the human being. On the fourth day the fertilized ovum of the monkey is merely a little ball of about sixteen cells, in the typical morular phase. On the eighth day it has become a blastocyst with a single-layered trophoblast. On the ninth day nidation begins and by the tenth day the amniotic cavity has formed, and the trophoblast has become bilaminated and lacunae have appeared. From this stage onward we can go direct to early human embryos for study. During the last three years a number of these specimens have been described. The two earliest include one described by Krafka (1942), a seven-day human embryo discovered in the tube, a fairly late ovum to be found outside the uterus, and a second embryo, to which Dr. Studdiford referred, the earliest of the Hertig-Rock collection. The latter is a seven-and-a-half-day embryo which has just started to be implanted, is not as yet covered by the epithelium of the uterus and is in the typical blastocele phase.

I would like to bring out in the discussion the question of judging the age of such specimens of early human ova. A certain degree of accuracy can be obtained from comparison with the monkey, but there must always be a small element of doubt in this method. If, however, the age is based on the menstrual history and the estimated time of ovulation, we are on perhaps more debatable ground. Ovulation presumably takes place about the fourteenth day, but a certain amount of variation must occur in this date. And how long after ovulation does fertilization occur? It is generally believed that not more than one day elapses between ovulation and fertilization, but possibilities of variation exist. The nidation of the fertilized human ovum may start, at the earliest, on the fifth day after ovulation, but it may be any time from the fifth to the ninth day. Therefore, in judging the age of an early embryo from the menstrual history alone, one might conceivably make a mistake of one or two days which, of course, in these early stages, may be very significant.

I do not think, however, from the teaching point of view, we are so interested in the exact age as in the stage of development of the embryo, in the steps of progress which have taken place in the various organ systems. It is from this standpoint that it is so important that more of such specimens should be collected to fill out the true history of human development. You gentlemen have the opportunity to make this material, when accidentally obtained, available for study. It should be sent in a properly fixed condition, preferably, I think, to the Carnegie Institution, where facilities are available for adequate sectioning and study.

I was interested to note that Hertig and Rock had found, out of a series of twelve early ova, seven normal which were all implanted on the posterior wall,

and five abnormal which were in each case implanted on the anterior wall. I am curious to know whether Dr. Studdiford feels that there is any relationship between the state of the embryo and the site of implantation. It would seem to me that in these cases it was a matter of pure chance.

DR. WILLIAM E. STUDDIFORD.—I think that Rock's observation that all normal implantations occurred on the posterior wall and all abnormal implantations occurred on the anterior wall must be just one of those runs of figures that occur in a small series of cases. We all know that we find perfectly normal pregnancies with the placenta on the anterior wall of the uterus as so often noted in cesarean section.

THE ERGOT ALKALOIDS

A Comparison of Ergonovine With the Total Alkaloids in Their Effects on the Puerperal Uterus

WILLIAM BICKERS, M.D., RICHMOND, VA.

TWO groups of ergot alkaloids are known to exist; the active substances including ergonovine, ergotoxine, ergotamine; and the inactive isomers including ergometrinine, ergotonine and others. The active alkaloids may be further divided into the (1) water soluble ergonovine which has a prompt but relatively fleeting oxytocic effect upon the uterus and (2) water insoluble ergotamine-ergotoxine group with a slower but more prolonged effect. Until the last seven years it was thought that the therapeutic potency of ergot resided exclusively in the water insoluble ergotamine-ergotoxine alkaloids. However, it should be noted that some years previously certain clinical observers had commented upon the fact that occasionally one did note some oxytocic effect in the water solutions of ergot but these observations were never reported or followed up. In 1929, Thompson, then at the University of Maryland, recognized the instability of the fluid extract of ergot and subsequently advised the use of a dry alkaloid salt, ergotamine tartrate.[1]

The foundation for all of our newer knowledge of ergot was laid by Chassar Moir at the University College Hospital in London, England.[2] Using an inflated rubber bag in the puerperal uterus he connected this by way of a rubber tube to a manometer which recorded the contractions of the uterus upon a kymograph. By the injection, separately, of the various alkaloids of ergot, he was able to demonstrate the relative therapeutic potencies of each. He concluded from these studies that both ergotamine and ergotoxine administered intramuscularly will produce strong uterine contractions; however, their action when given by this route is slow, often requiring fifteen to forty-five minutes for their effect to become apparent. In the second paper[3] Moir and Dale demonstrated for the first time that an aqueous extract of ergot given orally produced a marked stimulation of the puerperal uterus. They concluded that most of the oxytocic effect of ergot depended upon a yet

unidentified substance. In January, 1935, Thompson[4] confirmed the work of Moir by experiments upon the pregnant cat. In March, 1935, Dudley and Moir[5] reported the isolation of the truly active principle of ergot which they called ergometrine. In April of the same year, Kharasch and Legault reported independently their isolation of the same alkaloid which they called ergotocin. It should be said in passing, however, that in February, 1935, Davis, Adair, Rogers, Kharasch and Legault published a clinical report which was the basis for their laboratory report on ergotocine which followed several months later.[6]

Without doubt, this new water soluble alkaloid, now officially termed ergonovine in this country, is the most active and the most consistently potent of the ergot alkaloids. In contrast to the salts of other alkaloids such as ergotamine tartrate, it is effective when administered orally. Its prompt and consistent oxytocic action is very fleeting, however, while the slower and less dramatic effect of the ergotamine-ergotoxine group is prolonged and well sustained. The question arises as to whether in clinical practice, ergonovine should completely replace the other alkaloids of ergot or whether a combination of the short acting ergonovine with the longer acting total alkaloids should prove most desirable. Moir believes that ergonovine "has supplanted the alkaloids previously in use,"[7] while Thompson says "there is no single constituent of ergot that is representative of the full clinical oxytocic activity of ergot."[8] Guggisberg agrees in that he believes that the best clinical results will be obtained with a combination of ergonovine with the ergotamine-ergotoxine alkaloids.[9]

Clinical Comparison

Ergonovine and Total Alkaloids

One of the great contributions to obstetrics of the last decade came when Davis advocated the routine intravenous injection of ergonovine immediately after delivery of the fetal head. This investigator recommended the routine administration of 0.2 mg. of ergonovine maleate (Ergotrate, Lilly) as the shoulders were being delivered. He reported that immediate tonic contractions of the uterus invariably followed with early separation of the placenta and prompt expulsion. Blood loss was greatly reduced in all cases and the prompt delivery of the placenta provided a clear and dry field for the episiotomy repair. A series of other published reports soon followed confirming the good clinical results reported by Davis. After these favorable reports appeared, I adopted the routine injection according to the plan advocated by Davis and found that the average time interval in my cases between the intravenous administration of ergonovine and the delivery of the placenta was 3.1 minutes. This was the average in a consecutive series of 71 cases. Average blood loss in these patients was greatly reduced and the prompt delivery of the placenta facilitated the episiotomy repair. Although the results were far superior to any plan of oxytocic administration

previously employed, it was observed that a rather high incidence of delayed post-partum bleeding occurred. A small minority, 12 per cent in this group of 71 patients, had sufficient bleeding during the first two hours after delivery to require the second dose of ergonovine. In this bleeding group it was observed that the patient would leave the delivery room with a firm, contracted uterus only to be reported by the floor nurse on arrival in her room that the patient was bleeding and the uterus atonic. The delayed bleeding in this group was in no case alarming but this observation plus the well known fleeting action of ergonovine prompted an investigation of the short acting ergonovine in combination with the longer acting total alkaloids of ergot for intravenous injection during the placental stage of labor. An ampoule containing the total alkaloids of ergot was supplied by the manufacturer. This combination of ergonovine with the total alkaloids was given intravenously immediately after delivery of the fetal head to a consecutive series of 54 obstetric patients. The time between the injection and delivery of the placenta was carefully recorded with a stop watch and found to average 2.9 minutes. The shortest time was 30 seconds and the longest 8.5 minutes. No incarcerated placenta was encountered, and the blood loss in each patient was minimal, with the exception of one in whom the uterine response to the intravenous injection was delayed. Attempts were made to collect and measure the blood loss during and after the placental stage, but in my experience no satisfactory method of collecting the uterine blood loss has yet been devised and therefore the figures are not given. No cases in this series required a second dose of ergot for delayed bleeding within the first three hours after delivery and their uteri remained firm.

This clinical experience inspired the very definite impression that the routine use of ergonovine immediately after delivery of the fetal head provided a safe, effective, physiologic method of terminating the placental stage quickly and with minimal blood loss. It was also apparent that the short acting ergonovine, while highly satisfactory for the quick termination of the third stage, was followed within two hours of delivery by a disproportionately large group (12 per cent) of secondary uterine atonia which could be prevented by the use of ergonovine in combination with the total alkaloids of ergot instead of the ergonovine alone. In order to confirm or deny this clinical impression, a study of puerperal uterine contractions was undertaken, using an intrauterine balloon connected to a manometer.

Pharmacologic Comparison

Ergonovine and the Total Alkaloids of Ergot

Technique of Experiment.—A sterile rubber balloon of 80 c.c. capacity was inserted into the puerperal uterus within twenty-four hours after delivery. As previously reported, this is the period of maximum sensitivity of the puerperal uterus to oxytocics. The balloon was so

shaped that when distended with water its two "horns" filled the uterine cornua thereby anchoring it in place. The balloon was filled with sterile water until a distending pressure of 40 mm. was reached. This was the standard distending pressure used in all experiments as it has been learned by previous studies that this pressure is best suited for bringing out the uterine motility to a point where it can be readily recorded by the mechanical type of ink writing manometer used in these experiments.

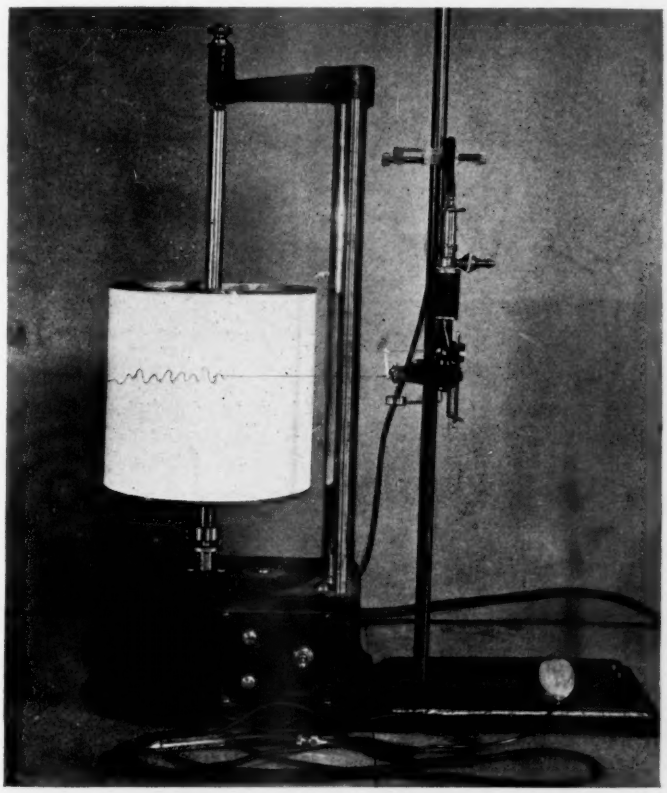

Fig. 1.

Often with lower pressures, no contractions can be recorded. It must therefore be emphatically stated that these tracings are comparative and do not necessarily represent the intrinsic motility of the puerperal uterus in the absence of a distending foreign body. The balloon is connected by way of an attached woven catheter to a rubber tube with the mechanical ink writing manometer so arranged that the contractions of the uterus are graphically recorded on the revolving kymograph. Trauma incident to the introduction of the balloon always throws the uterus into spasm which subsides within several minutes; tracings were started after the spasm had disappeared. The time intervals on the tracings were recorded by an electric timer. Injections of the solutions under investigation were made intravenously at the points indicated by the arrows, the arrow being the point at which the injection was completed. The ergonovine employed in these experiments was in each instance the 1 c.c. ampoule of ergonovine maleate (Ergotrate-Lilly) 0.2

mg. The total alkaloids employed in these experiments was in each instance the 1 c.c. ampoule of total alkaloids of ergot (S. S. Ergot Alkaloids-Upjohn). This ampoule contains 1.12 mg. of total alkaloids calculated as ergotoxine, 0.78 mg. of water insoluble alkaloids calculated as ergotoxine, and 0.183 mg. of water soluble alkaloids calculated as ergonovine. In this combination it is impossible to calculate the exact amount of ergonovine but the total water soluble alkaloids calculated as ergonovine is determined by the Hampshire-Page method of assay. Each c.c. of this solution contains approximately 0.17 mg. of ergonovine which is equivalent theoretically to 0.2 mg. of ergonovine maleate (Fig. 1).

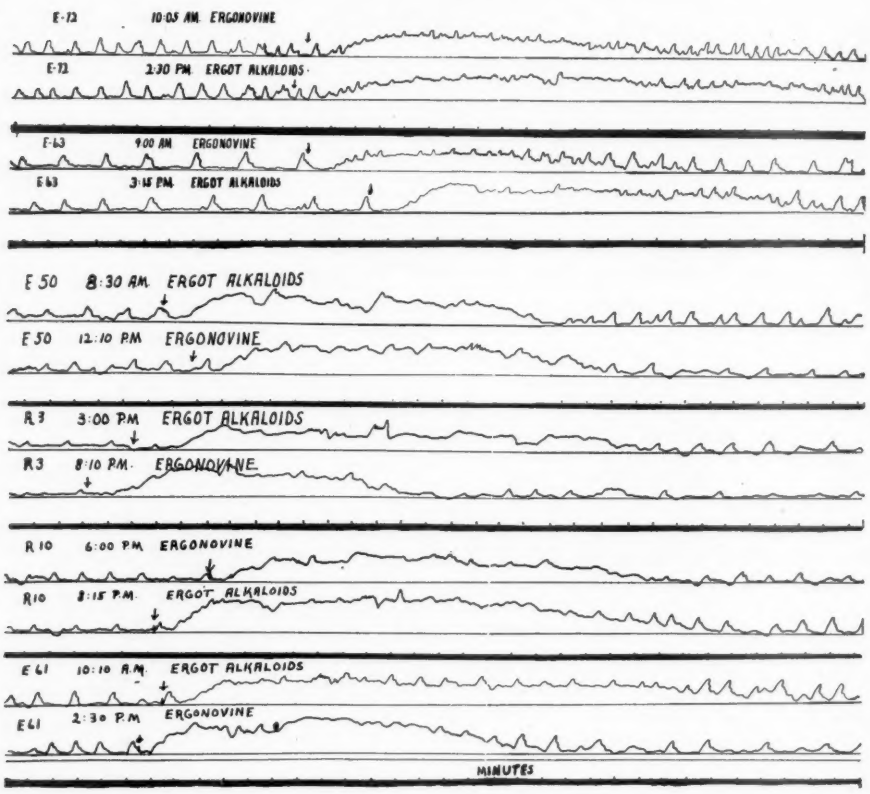
E-72 10:05 AM. ERGONOVINE
E-72 2:30 PM. ERGOT ALKALOIDS
E-63 9:00 AM. ERGONOVINE
E-63 3:15 P.M. ERGOT ALKALOIDS
E 50 8:30 AM. ERGOT ALKALOIDS
E 50 12:10 P.M. ERGONOVINE
R 3 3:00 P.M. ERGOT ALKALOIDS
R 3 8:10 P.M. ERGONOVINE
R 10 6:00 P.M. ERGONOVINE
R 10 8:15 P.M. ERGOT ALKALOIDS
E 61 10:10 A.M. ERGOT ALKALOIDS
E 61 2:30 P.M. ERGONOVINE
MINUTES

Fig. 2.—Graphs showing comparison between effects of ergonovine alone and with total alkaloids on the puerperal uterus. Case E-72, Ergonovine Effect, 12 minutes, no change in motility. Total Alkaloids Effect, 22 minutes, marked increase in motility. Case E-63, Ergonovine Effect, 12 minutes, no change in motility. Total Alkaloid Effect, 16 minutes, marked increase in motility. Case E-50, Ergonovine Effect, 16 minutes, slight stimulation to motility. Total Alkaloids Effect, 15 minutes, marked increase in motility. Case R-3, Ergonovine Effect, 12 minutes, moderate stimulation to motility. Total Alkaloids Effect, 18 minutes, marked increase in motility. Case R-10, Ergonovine Effect, 17½ minutes, no effect on motility. Total Alkaloids Effect, 22½ minutes, marked increase in motility. Case E-61, Ergonovine Effect, 15 minutes, no effect on motility. Total Alkaloids Effect, 24 minutes, marked increase in motility.

Outline of the Study.—Tracings shown in this report were obtained by the technique just described from the puerperal uteri of 12 normal primiparas delivered at term. In all of them the labors were uneventful, no sedation or other medication was given during labor and the only anesthesia employed was procaine hydrochloride pudendal nerve

block for the performance of the outlet forceps. Epinephrine was omitted from the procaine and no oxytocic was given to the patient prior to the experiments. All of the tracings were taken on the first day postpartum, usually within a few hours after delivery. The initial tracing was often taken immediately after delivery of the placenta and the second tracing on the same patient several hours later, after the effect of the first experiment had disappeared. Since the response of different uteri to oxytocics is quite variable, it was necessary to compare the effects of ergonovine alone and the total alkaloids on the same patient. Some received the ergonovine for the initial experiment, in others the procedure was reversed.

Explanation of Tracings.—Uterine contractions were recorded on the first day post partum in 12 normal primiparas. The tracings obtained on 6 of these patients are shown as fair samples of the entire group. It will be noted that each patient received one dose of ergonovine and one dose of total ergot alkaloids as previously described. The first tracing was taken usually about one hour after delivery, the effect of the intravenous injection of ergonovine or ergot alkaloids being recorded at this time. After a period of time indicated on the tracings, the ergot preparation not given at the initial experiment was given for comparison. Tonic contractions followed promptly the injection of the ergonovine or total alkaloids in every case. This marked oxytocic effect became apparent in thirty to ninety seconds in all cases and no difference in reaction time between ergonovine and the total alkaloids could be elicited. However, in the duration of the response there was a marked difference. For all of the tracings the average duration of the total alkaloid response was twenty minutes while that for ergonovine was 14 minutes. In half of the patients a prolongation of the total alkaloid effect is demonstrable and in the other half the ergonovine and total alkaloids effects are about the same. In one case was the ergonovine effect longer than the total alkaloids effect. The most consistent difference between the two was demonstrated in the pattern of uterine motility which followed the tonic response. It will be seen from the tracings that following the tonic contractions induced by the total alkaloids, there was in each case a hypermotility of the myometrium as shown by the more rapid rate and increased amplitude of the contractions. The ergonovine tracings occasionally show some tendency to this increased uterine contractility but it is not constant; it is the rule in the total alkaloid tracings.

Conclusions

1. Ergonovine, the water soluble alkaloid of ergot, has a prompt but fleeting oxytocic effect upon the puerperal uterus. Given intravenously, there is a tonic response in thirty to ninety seconds which persists on the average of 14 minutes. Following the tonic response, there is no consistent alteration in the pattern of uterine contractions from that seen before the ergonovine was given. Clinically the intravenous administration of ergonovine (0.2 mg.) just after delivery of the fetal head is followed by expulsion of the placenta in 3.1 minutes (71 cases) with minimal blood loss. Uterine atonia follows in 12 per cent of the patients, requiring a second injection of the oxytocic within two hours of delivery.

2. Total alkaloids of ergot, a combination of 0.17 mg. of ergonovine with 1.12 mg. of total alkaloids calculated as ergotoxine, 0.78 mg. of

water insoluble alkaloids calculated as ergotoxine, has a prompt and also a sustained oxytocic effect upon the puerperal uterus. Given intravenously there is a tonic response in thirty to ninety seconds which persists for the average of twenty minutes. In these experiments 50 per cent of the uteri gave a more sustained response to the total alkaloids than to ergonovine alone. In some cases the effect is almost twice that of ergonovine alone. In one case did the oxytocic response of a uterus to ergonovine alone exceed that of the total alkaloids. After the tonic response has disappeared, there is a consistent increase in the rate and amplitude of the uterine contractions which persists for about two hours.

Clinically the intravenous injection of the total alkaloids immediately after delivery of the fetal head is followed by delivery of the placenta in 2.9 minutes (54 cases) with minimal blood loss. Uterine tonus was maintained in all cases and none required a second dose of the oxytocic within two hours.

References

1. Thompson, M. R.: J. Am. Pharm. A. **20**: 1027, 1931.
2. Moir, C.: Brit. Med. J. **2**: 1022, 1932.
3. Moir, C., and Dale, H. H.: Brit. M. J. **2**: 119, 1932.
4. Thompson, M. R.: J. Am. Pharm. A. **24**: 24 and 185, 1935.
5. Dudley, H. W., and Moir, C.: Brit. M. J. **1**: 520, 1935.
6. Davis, M. E., Adair, F. L., Rogers, G., Kharasch, M. S., and Legault, R. R.: Am. J. Obst. & Gynec. **29**: 155, 1935.
7. Moir, C.: Brit. M. J. **2**: 799, 1936.
8. Thompson, M. R.: Personal communication to Beecham, C. T., and Heyl, W. M., February 12, 1935.
9. Guggisberg, H.: Helvetia Med. Acta **4**: 13, 1937.
10. Davis, M. E.: Am. J. Surg. **48**: 154, 1940.
11. Bickers, William: Am. J. Obst. & Gynec. **44**: 481, 1942.

THE VALUE OF PELVIORADIOGRAPHY IN THE MANAGEMENT OF DYSTOCIA*

ARTHUR WEINBERG, M.D., AND SAMUEL J. SCADRON, M.D.
NEW YORK, N. Y.
(From the Departments of Radiology and Obstetrics, Beth Israel Hospital)

IT IS generally acknowledged that the more accurate estimation of the qualitative and quantitative capacities of the obstetric pelvis has played an important role in the decrease in the maternal and fetal morbidity and mortality which has occurred in the last decade. Obstetricians have come to realize that pelvic estimations by the ordinary methods of external and internal pelvimetry, while of some value, are not accurate indicators of the linear measurements of the pelvis and moreover fail to give a true picture of the architectural features of the pelvis which are at least as important as the measurements themselves.

Dippel and Hodges[11] have shown that the external conjugate is not a true guide to the length of the true conjugate. Jacobs proved that Smellie's rule of subtracting 1.5 to 2.0 cm. from the diagonal conjugate to estimate the true conjugate is accurate in only 10 per cent of the cases studied. Scadron and Rappaport[16] have shown that the roentgen measurements are consistently greater than the clinical measurements and that in many cases clinically contracted pelves were proved to be ample by x-ray pelvimetry and subsequent delivery. The superiority of roentgen pelvimetry to clinical pelvimetry is emphasized by references to the following tables which summarize a comparative study of 350 consecutive cases x-rayed 10 days before term as a routine between 1936 and 1938 (Table I). Of 257 cases in which the clinical estimation and x-ray pelvimetry agreed that the pelvis was ample, 253 were proved ample by subsequent delivery. This indicates an accuracy in such circumstances of 98.4 per cent. Forty-four cases in which the clinical and radiologic prognosis agreed that a pelvis was contracted were confirmed, and 39 proved, showing an accuracy of 88.6 per cent.

TABLE I. DIAGNOSIS VS. CLINICAL RESULTS

DIAGNOSIS	NO. OF CASES	PROVED AMPLE	PROVED CONTRACTED	PERCENTAGE CORRECTED
1. Clinic: ample	257	253	4	Clinic 98.4
X-ray: ample				X-ray 98.4
2. Clinic: contracted	30	25	5	Clinic 16.6
X-ray: ample				X-ray 83.4
3. Clinic: ample	19	5	14	Clinic 26.3
X-ray: contracted				X-ray 73.7
4. Clinic: contracted	44	5	39	Clinic 88.6
X-ray: contracted				X-ray 88.6

*Read at a meeting of the Section of Obstetrics and Gynecology, New York Academy of Medicine, Feb. 23, 1943.

If, however, a pelvis was classified clinically as contracted, and ample by pelvioradiography, as occurred in 30 instances, and subsequent events proved the pelvis ample in 25 cases, then the x-ray was correct in 83.4 per cent and the clinical judgment in only 16.6 per cent. Conversely, in the 19 cases in which the clinical examination revealed an ample pelvis but the x-ray showed a contracted pelvis, the pelves proved contracted in 14 cases; the x-ray being 73.7 per cent correct and the clinical judgment in only 26.3 per cent. In other words when the clinical and x-ray prognosis agree, the accuracy of prognosis is highest but when they disagree the x-ray prognosis is much more to be trusted; as a matter of fact it is three times as accurate in such circumstances.

A comparative study was also made of the accuracy of diagnosis by clinical and x-ray pelvimetry. By clinical pelvimetry, if a pelvis was considered contracted this proved to be correct in only 59.1 per cent of the cases whereas if it was considered ample the prognosis was correct in 93.5 per cent (Table II).

TABLE II. ACCURACY OF DIAGNOSIS

	DIAGNOSIS	NO. OF CASES	PROVED AMPLE	PROVED CONTRACTED	PERCENTAGE CORRECT
Clinic	Contracted	74	30	44	59.1
X-ray	Contracted	63	10	53	84.1
Clinic	Ample	276	258	18	93.5
X-ray	Ample	287	278	9	97.0

By pelvioradiography if a pelvis was considered contracted, this proved to be correct in 84.1 per cent while if it were considered ample, 97.0 per cent accuracy was obtained. In other words, the diagnosis of a contracted pelvis is not as accurate as the diagnosis of an ample pelvis but the x-ray is a great aid in properly diagnosing contracted pelves.

Material

Since 1938 we have made pelvioradiographic studies only when dystocia was anticipated before labor, or arose unexpectedly during labor. Dystocia was anticipated if the pelvimetry done in the prenatal clinic was indicative of a contracted pelvis or if the past history of a multipara led us to believe dystocia was a factor in her previous obstetrical history. Any patient with a diagonal conjugate of 11.5 cm. or less, or who showed evidence of physical or pelvic android tendencies, was also put in the expected dystocia group. This group of cases were x-rayed at term or early in labor. In those cases in which favorable clinical prognosis was made, but in which engagement failed to occur, malpresentation was evident, or labor failed to progress satisfactorily, x-rays were taken during labor and repeated if necessary. This study consists of 280 consecutive cases studied by pelvioradiography between 1938 and 1941 because of fear of dystocia, either anticipated or unexpected. We have found the procedure of pelvioradiography of great value in the management of these cases.

Method

Roentgenological Technique.—We use a combined method of pelvioradiography which includes the best features of various methods of

roentgen pelvimetry, pelvicephalometry and determination of pelvic architecture.

We take five films: a 14 by 17 anteroposterior and lateral at 30 inches. Included in the lateral is an isometric scale which is applied to the midsagittal plane according to the Thoms principle.

The anteroposterior film is studied for presentation, position, number, attitude, size and maturity of the fetus. The interspinous diameter and the circumference of the skull are measured. On the lateral view the anteroposterior diameter of the inlet and the circumference of the skull are measured. These four measurements are corrected for distortion and converted into volumetric equivalents for comparison by the Ball nomogram. In addition, the true conjugate, posterior sagittal of the midpelvis and outlet, pubotuberous diameter, and depth of the pelvic axis are determined by the Thoms isometric scale.

A pair of stereoscopic pelvic inlet films are taken with the lumbosacral angle raised, and studied in the precision stereoscope built by Dr. Myron Schwarzshild, for the determination of pelvic architecture, fetal pelvic relationships and to check the anteroposterior and greatest transverse diameter of the inlet measurements. A 45-degree angle anteroposterior film is taken for the study of the subpubic angle, side walls, sacrum, and ischial spines. We thus have a triple check on the most important diameter, the true conjugate, and a double check on all other measurements.

Prognosis

The obstetric prognosis as defined in this paper is based on what we observe in the films: on the pelvimetry, cephalopelvic relationship, pelvic architecture and fetal attitude. To arrive at the true obstetric prognosis, the obstetrician must combine the x-ray prognosis with the clinical prognosis. As far as the estimation of the pelvis is concerned the x-ray is more accurate. However, the estimation of uterine force, cervical rigidity, soft part dystocia, size of head, age and condition of the patient is entirely based on clinical experience and judgment and perhaps is as important as the pelvic factor in a great many cases.

Classification of Pelves

All pelves were classified according to their architectural features as outlined by Caldwell, Moloy, and D'Esopo[4-8]: gynecoid, android, anthropoid anl platypelloid.

Classification of Radiologic Prognosis

On the bases of the pelvic size and architecture, fetal pelvic relationships and treatment recommended, all cases were classified into one of four prognostic groups as follows: good, fair, guarded and poor, on the bases of criteria listed in Table III. The treatment recommended and the outcome expected from consideration of the radiologic features alone, are included. The fetal pelvic relationship includes a consideration of the type of synclitism, the manner of engagement, the amount of flexion and the pelvic architecture. Groups A & B are normal pelves and C & D are considered contracted.

Results (Table IV)

Group A.—Consists of those cases with no disproportion and a good prognosis. Spontaneous delivery is the rule. There were 173 cases or

TABLE III

GROUP	PROG-NOSIS	A. P.	A. P. PLUS TRANS.	FETAL PELVIC RELATION	TREATMENT	OUTCOME EXPECTED
A	Good	cm. above 10.5	cm. 24	No disproportion	Labor	Spont. delivery is the rule
B	Fair	10-10.5	22-24	Borderline disp.	Test labor	Vaginal delivery is usual
C	Guarded	9-10	20-22	Relative disp.	Short trial labor	Cesarean section probable
D	Poor	7.5-9.0	Below 20	Absolute disp.	Cesarean section	Cesarean section necessary

62 per cent of the entire series in this group. In other words, in more than half the cases in which dystocia was feared, the x-ray indicated a very favorable outcome with vaginal delivery. Considering that low forceps are often elective it was decided to consider them as non-operative, and to judge all other forceps, operations, cesarean sections and other vaginal maneuvers as operative. The number of cases that required operative deliveries in group A was 35 and this amounted to 20 per cent of the group; the remaining 80 per cent delivered either spontaneously or with low forceps.

There were 7 stillbirths, two of which died before delivery, one from pneumonia, the other from maternal toxemia and sepsis. The other five stillborns died of intracranial hemorrhage sustained during vaginal delivery. If these babies were delivered by section they probably would have survived; therefore we probably were wrong in five instances in advising vaginal delivery.

The five cases sectioned in this group were sectioned for extrapelvic indications: placenta previa, diabetes, pelvic tumor and two cases of breech in elderly primiparas. We gave a correct prognosis in 168 cases and a wrong one in 5 cases; a correct prognosis of 97 per cent.

Group B.—Includes cases with borderline disproportion and a fair prognosis. A test of labor is usually recommended and vaginal delivery is the rule. There were 55 cases or 19 per cent of the entire series in this group. Operative delivery was necessary in 56 per cent. Midforceps was the most frequent operation and was performed in almost one-third of the cases. The incidence of operative vaginal deliveries is much higher than in group A and cesarean section had to be performed in 16 per cent of the cases. Cesarean section is often necessary in this group if the baby is over 9 pounds. Nine cases required cesarean sections, all of which were low cervical sections following a test of labor. Eight of these babies weighed over 9 pounds. It is difficult to predict the weight of the baby by x-ray because the calcification doesn't change much, but the weight increases ½ pound a week in the last month. With average sized babies the test of labor might have resulted in a vaginal delivery. The chief value of pelvioradiography in borderline cases is to indicate that a possible section should be kept in mind and not to jeopardize the possibility of performing a safe section during labor by waiting too long or by manipulation.

There was one stillborn in this group, and it was from intracranial hemorrhage during a midforceps delivery in an android pelvis. We

TABLE IV. MANNER OF DELIVERY ARRANGED ACCORDING TO PELVIC RADIOGRAPHIC PROGNOSIS

PROGNOSIS*	TOTAL	SPONT.	LOW FORCEPS	MID-FORCEPS	BREECH EXTRAC.	VERSION	CRANIOT.	CESAREAN SECTION	TOTAL OPERATIVE	% OPERATIVE	TOTAL STILLBIRTHS	WRONG PROGNOSIS	CORRECT PROGNOSIS	% CORRECT
A	173	75	63	14	13	2	1	5	35	20	7	5	168	97
B	55	11	13	17	3	2	0	9	31	56	1	1	54	98
C	27	2	2	4	0	0	0	19	23	85	4	0	27	100
D	25	0	0	2	1	0	0	22	25	100	3	0	25	100
Total	280	88	78	37	17	4	1	55	114	40	15	6	274	97.8

*A, good; B, fair; C, guarded; D, poor.

were therefore wrong once and correct 54 times resulting in a correct prognosis in 98 per cent.

Group C.—This was the group with a guarded prognosis. Relative disproportion was evident and a short trial of labor with early section was advised. Ten per cent or 27 cases were in this group. Twenty-three cases or 85 per cent required operative deliveries. In 19 cases a cesarean was performed. There were 4 stillborns in the 8 vaginal deliveries. One was a spontaneous premature stillbirth. The other three were due to delivery. In all 3 cases a cesarean section was considered probable and was advised after a very short trial of labor. In these three cases the advice was disregarded and difficult vaginal delivery attempted after long labor. We made the correct prognosis in all of these cases or 100 per cent.

Group D.—This consisted of those 25 cases or 9 per cent of the series who had poor prognosis, absolute disproportion, and in which an elective or immediate section was necessary. Twenty-three of the 25 cases were either android or platypelloid types. In 22 cases a successful section was performed. In the three cases in which a vaginal delivery was attempted, stillbirths resulted.

In the entire series of 280 cases a correct prognosis was given in 274 cases, or 97.8 per cent. A favorable prognosis was given in 173 cases and 166 either delivered spontaneously or by low forceps, many of which were elective or prophylactic. Of the entire series only 40 per cent required operative delivery; this indicates the conservative effect of pelvioradiography.

Anthropoid Pelvis.—The long oval pelvis, now called anthropoid, was conspicuous in this series of dystocia cases, by its rarity and by its failure to cause significant difficulty. Twenty-two cases, or 8 per cent, of the entire series were either true or mixed anthropoid types. No anthropoid case had to be given guarded or poor prognosis and the results justified our optimism; only 12 per cent were operative and these were all vaginal deliveries. No cesarean sections were necessary. There were no stillbirths and the correct prognosis was made in 100 per cent of the cases.

Gynecoid Pelvis.—The gynecoid, female or round pelvis was the most frequent type encountered in this series, but its percentage incidence was less than in our obstetrical service at large. Of the 136 gynecoid pelves, 124 were true gynecoid, and 12 gynecoid with an anthropoid tendency. The mixed group all had a good or fair prognosis and were considered with the true gynecoid for the statistics of the total gynecoid series. From Table V it can be seen that most of the gynecoid cases were classed in the groups with a good prognosis and only 11 per cent in groups with a guarded or poor prognosis. The operative incidence was 32 per cent. Three of the 12 stillborns were in this group. The incidence of stillbirths was 2.2 per cent. A wrong prognosis was made in 2 cases and a correct one in 134. We were correct in 98 per cent of our attempts in the gynecoid series. In no case of a gynecoid pelvis in which section was recommended on the basis of relative or absolute disproportion was a live baby delivered vaginally, even though out of 13 such cases, 10 had trial of labor or attempted vaginal delivery.

Android Pelvis.—The android, male or funnel pelvis in its true and mixed form made up 34 per cent of the series. Its incidence in the dystocia series is, as expected, greater than in the obstetrical service of the hospital at large. One-third of the android cases were given a

TABLE V. PROGNOSIS AND RESULTS ACCORDING TO PELVIC ARCHITECTURE

PELVIC TYPE	GENERAL INCIDENCE %	DYSTOCIA INCIDENCE NO.	DYSTOCIA INCIDENCE %	A* NO.	A* %	B* NO.	B* %	C* NO.	C* %	D* NO.	D* %	OPERATED NO.	OPERATED %	STILLBORN NO.	STILLBORN %	CORRECTED STILLBORN STATISTICS NO.	CORRECTED STILLBORN STATISTICS %	WRONG PROGNOSIS	CORRECT PROGNOSIS	% CORRECT
Anthropoid	17	22	8	25	96	1	4	0	0	0	0	3	12	0	0	0	0	0	22	100
Gynecoid	56	136	49	107	78	16	11	11	8	2	3	53	32	5	3.6	3	2.2	2	134	98.5
Platypelloid	5	26	9	7	32	7	32	1	4	7	32	9	41	1	4.0	0	0	0	26	100
Android	22	96	34	34	35	31	32	15	16	16	17	49	51	9	9.3	9	9.3	4	92	96.0
Total		280	100	173	62	55	19	27	10	25	9	114	40	15	5.3	12	4.3	6	274	97.9

*A, good; B, fair; C, guarded; D, poor.

guarded or poor prognosis and operative deliveries were necessary in 51 per cent of the cases. In four cases in which a favorable prognosis was given stillborn vaginal deliveries resulted. A correct prognosis was given in 96 per cent of the android series. The highest incidence of stillbirths (9.3 per cent) occurred in this series.

A comparison of the true android, to the mixed android pelvis failed to influence either the prognosis or the ease of parturition to any large extent; consequently all android pelves were classified together in this series.

Platypelloid Pelvis.—The flat pelvis occurred in 9 per cent of the dystocia series. This is about twice as frequent as in the hospital obstetrical service at large. Of the 26 cases classified as platypelloid, one-third were given a poor or guarded prognosis. The operative incidence was 41 per cent or 9 cases, all except one of which were cesarean sections. This confirms our previous impression: that if a flat pelvis is to give trouble it usually will do so early, and will interfere with engagement and necessitate an early section; however, if it fails to give trouble at the inlet it is rare that it will cause subsequent serious difficulty. The only stillbirth in this group was a spontaneous premature delivery which was due to extrapelvic cause (Table V). It is relatively easy to prognosticate this group and we were correct in all twenty-two cases or 100 per cent.

Stillbirths

In this series of 280 cases of dystocia there were 15 stillbirths, an incidence of 5.3 per cent. This is slightly above the usual hospital figure, but is not high for a dystocia series. Three of the babies died of conditions unrelated to delivery, namely, maternal sepsis and toxemia, pneumonia, and prematurity. Of the other 12 cases cesarean section was advised in 6 but this advice was disregarded and difficult vaginal deliveries resulted in stillbirths. The other six were advised to have vaginal deliveries but suffered the same fate. These are our six mistakes. The methods of delivery of the 15 stillbirths were as follows: low forceps 3, midforceps 7, breech extraction 3, craniotomy 1, and spontaneous 1.

No correction is made for the fact that soft part dystocia, poor uterine force or lack of skill played a part in these mistakes, but in some cases they were undoubtedly operative.

Choice of Forceps

In most cases ordinary pelvic curved forceps such as the Simpson, Elliott, solid blade and Williamson modifications were used. The Kielland forceps were used seven times. Two stillbirths occurred during attempts at rotation at the level of arrest in android pelves. Possibly the choice of Barton or Kielland forceps with extraction to the outlet before rotation would have given better results, because it has been shown that the maneuver to be used in cases of arrest varies with the pelvic architecture involved; and that in flat and android pelves only low rotation is safe.

Cesarean Section

Cesarean was resorted to 55 times or in 19 per cent of the cases in this dystocia series. This is twelve times as high as the usual incidences in our hospital in general, but is not high for a series of dystocia cases.

In those cases with a good prognosis, section was done five times, all for extrapelvic indications. In the borderline group with a fair prognosis there were 9 sections, all performed after a trial of labor failed to produce sufficient progress. In almost all of these the baby was of large size. In 27 cases with relative disproportion there were 19 sections although it was advised in 4 additional cases. In the 25 cases of absolute disproportion for all of which a section was recommended, failure to perform it in three cases resulted in three stillbirths.

Forty-four per cent of the cesareans were in gynecoid pelves, 43 per cent in android and 13 per cent in platypelloid. There were none required in the anthropoid group.

Maternal Morbidity and Mortality

Aside from a number of cases of self-limited puerperal infection, the only significant morbidity resulted from a difficult forceps operation. This was a case of a patient with a true android pelvis and absolute disproportion for which a section was recommended. This advice was not followed and the midforceps operation with solid blades, Williamson and Barton forceps resulted in a vesicovaginal fistula and stillbirth.

There was no maternal mortality in this series.

Summary

A series of 280 obstetric cases in which dystocia was expected were studied by pelvioradiography as an aid in determining the obstetrical prognosis and treatment. The cases were classified in four groups: no disproportion, borderline, relative, and absolute disproportion; and the prognosis was good, fair, guarded and poor, respectively. Treatment recommended was based on the above considerations.

1. The roentgen prognosis was correct in 97.9 per cent.
2. As the prognosis became worse the incidence of operative deliveries increased.
3. Cesarean section was necessary for good results when poor prognosis was given by x-ray pelvimetry.
4. In 52 cases in which cesarean was considered likely, it was performed in 41 and should have been performed in 7 more as indicated by disastrous results following vaginal delivery.
5. The conservative influence of pelvioradiography in a dystocia series was shown by the fact that only 114 or 40 per cent required operative delivery.
6. The android and platypelloid pelves were frequently found among the cases in which poor prognosis was given.
7. The anthropoid pelves were all given a favorable prognosis, and subsequent events proved this confidence justified.
8. The gynecoid pelvis was the most difficult to evaluate correctly and the size of the pelvis was often the chief guide. There was an increase in operative deliveries in the following order: anthropoid, gynecoid, platypelloid and android.
9. Half of the stillbirths could have been avoided if the radiologic advice had been followed.
10. The cesarean operation was more accurately limited to those cases in which it was essential.

Conclusion

A correct obstetrical prognosis based on pelvioradiography was possible in 97.9 per cent of a series of cases in which dystocia was expected. Since correct treatment depends on accurate diagnosis and prognosis we feel that pelvioradiography is of great value in the management of dystocia.

Lt. Emanuel Dickler, U. S. Army, former resident in radiology at Beth Israel Hospital, New York City, rendered invaluable aid in reading some of these films. Drs. I. Seth Hirsch and Arthur Bendick, chiefs of the department of radiology at Beth Israel, were helpful in prognosticating some of the doubtful cases. Dr. Murray Resnick, resident in radiology, supervised the technical features of the pelvimetry.

Miss Edith Zwerling and Miss Eilene Eisenberg were helpful in the preparation of the statistical aspects of the paper.

References

1. Ball, Robert P.: Surg., Gynec. & Obst. **62**: 798, 1936.
2. Ball, Robert P.: Radiology **31**: 188, 1938.
3. Caldwell, W. E., and Moloy, H. C.: AM. J. OBST. & GYNEC. **26**: 479, 1933.
4. Caldwell, W. E., Moloy, H. C., and D'Esopo, D. Anthony: AM. J. OBST. & GYNEC. **28**: 482, 1934.
5. Caldwell, W. E., and Moloy, H. C.: AM. J. OBST. & GYNEC. **28**: 824, 1934.
6. Caldwell, W. E., Moloy, H. C., and D'Esopo, D. Anthony: AM. J. OBST. & GYNEC. **30**: 763, 1935.
7. Caldwell, W. E., Moloy, H. C., and D'Esopo, D. Anthony: AM. J. OBST. & GYNEC. **32**: 727, 1936.
8. Caldwell, W. E., Moloy, H. C., D'Esopo, D. Anthony: AM. J. OBST. & GYNEC. **36**: 928, 1939.
9. Friedman, Lewis J., Michels, L. M., and Rossitto, H. F.: Surg., Gynec. & Obst. **61**: 735, 1935.
10. Hodges, Paul C.: Am. J. Roentgenol. **37**: 644, 1933.
11. Hodges, P., and Dippel, A.: Surg., Gynec. & Obst. **70**: 421, 1940.
12. Jarcho, Julius: AM. J. OBST. & GYNEC. **10**: 35, 1925.
13. Jacobs, J. Bay: AM. J. OBST. & GYNEC. **43**: 267, 1942.
14. Moloy, H. C.: Am. J. Roentgenol. **39**: 111, 1933.
15. Scadron, Samuel J.: Surg. Gynec. & Obst. **40**: 697, 1925.
16. Scadron, Samuel J., and Rappaport, Emanuel M.: J. A. M. A. **112**: 2492, 1939.
17. Schumann, Wm.: AM. J. OBST. & GYNEC. **28**: 497, 1934.
18. Steele, Kyle B., Wing, Lucius H., and McLane, Charles M.: AM. J. OBST. & GYNEC. **35**: 938, 1938.
19. Steele, Kyle B., and Javert, Carl T.: AM. J. OBST. & GYNEC. **43**: 600, 1942.
20. Thoms, H.: J. A. M. A. **92**: 1515, 1929.
21. Thoms, H.: AM. J. OBST. & GYNEC. **42**: 987, 1941.
22. Weinberg, Arthur: New York State J. Med. **40**: 1530, 1940.
23. Weinberg, Arthur: West. J. Surg. **48**: 227, 1940.
24. Williams, J. W.: Textbook of Obstetrics, New York, 1930, D. Appleton-Century Co., Inc.

THE TREATMENT OF SYPHILIS IN PREGNANCY BY THE FIVE-DAY MASSIVE DOSE METHOD*

HERBERT RATTNER, M.D., CHICAGO, ILL.†

(From the Department of Dermatology, Cook County Hospital and the Northwestern University Medical School)

THE treatment of early syphilis by the method of Hyman, Chargin and Leifer[1] in which massive doses of mapharsen are administered by continuous intravenous drip was begun as a clinical experiment at the Cook County Hospital in August, 1940.

Early in our study an unusual opportunity to observe the effects of massive dose therapy on both mother and fetus in utero occurred when a young primipara in beginning labor was found to have a syphilitic chancre on the labium. Treatment was instituted immediately and the patient had received two complete days of treatment with a total dosage of 0.48 Gm. of mapharsen when she was delivered of a full-term, normal infant. The third-day-treatment was resumed the next morning and was continued through until the end of the five-day period with no ill effects.

Shortly thereafter a young woman in her seventh month of pregnancy reported to the clinic with an eruption of secondary syphilis. She, too, was given the prescribed course and at the end of the five-day period had received the full dose of 1,200 mg. of mapharsen. Two months later she was delivered of a full-term, normal infant who is now 21 months old, in good health and free so far of any evidence of syphilis.

Encouraged by the results in these two cases, the method was then applied to other cases of pregnancy complicated by syphilis and to date, the five-day treatment has been administered to twenty-seven pregnant women, four of whom had primary lesions, fifteen eruptions of secondary syphilis, and eight latent syphilis of less than four years' duration. The majority of these patients were in the fifth month of pregnancy or later, and none of them had received any previous antisyphilitic treatment.

Technique

At the Cook County Hospital up to January, 1943, 481 cases of early syphilis in both men and women have been studied, 421 of whom have been treated by the massive dose method. In the beginning of the study the technique of Hyman et al. was adhered to carefully: a daily dose of 240 mg. of mapharsen dissolved in 2,000 c.c. of five per cent glucose solution administered by intravenous drip on each of five consecutive days. At the end of the first year of the study, it was observed that the best results were obtained in patients who had reported for treat-

*Presented before the Chicago Gynecological Society, February 19, 1943.

†This study was sponsored by the Department of Public Health, State of Illinois, R. R. Cross, M.D., Director; Herman Soloway, M.D., Venereal Disease Control Officer; with the support of the U. S. Public Health Service.

ment very early in the course of their infections; and that the failures, though few, that had occurred were all in patients who had been treated for secondary-stage eruptions. The treatment was then modified in an effort to reduce this incidence of failures. Thereafter patients with secondary syphilis were given, in addition to the mapharsen, a daily intramuscular injection of two c.c. of soluble sodium bismuth tartrate, each dose representing 22 mg. of metallic bismuth. Of the group herein reported, seventeen of the pregnancy cases have been treated by this modified method.

Results

One of the twenty-seven patients treated was lost from our observation. In the twenty-six others the pregnancy has terminated with the birth of a full-term, apparently normal infant in every case with but one exception; and in that case there was reason to believe that the mother, after having been treated successfully for secondary-stage syphilis in her fifth month of pregnancy, had then been reinfected or superinfected at a time most unfortunate for the infant. The record was as follows:

MOTHER		INFANT	
11/ 1/41	Secondary syphilis Pregnant five months Five-day treatment with arsenic-bismuth Kahn quantitative 20 units		Cord blood negative
11/ 8/41	Kahn quantitative 20 units	3/ 9/42	Kahn quantitative 3 units Roentgenogram of long bones normal
11/13/41	Kahn quantitative 4 units	3/16/42	Kahn quantitative 3 units
11/27/41	Kahn quantitative 1 unit	3/20/42	Kahn quantitative 1 unit
12/ 4/41	Kahn quantitative negative	3/25/42	Roentgenographic changes which pediatricians thought were syphilitic; radiologists thought they were not syphilitic
12/11/41	Kahn quantitative negative In this period Dec. 4 to Dec. 11, she was exposed on several occasions to a man undergoing routine treatment for early syphilis at another clinic.	3/31/42	Blood test negative
January, 1942.	Failed to report for examination	4/ 7/42	Blood test negative
2/ 9/42	Kahn quantitative 40 units	4/16/42	Blood test negative
2/27/42	Was delivered of a full-term infant	5/ 5/42	Kahn quantitative 3 units
3/ 5/42	Kahn quantitative 120 units	6/26/42	Kahn quantitative 560 units

Incidentally, the mother had apparently acquired both of her infections from the same man. He had been receiving the conventional syringe method of treatment but had been irregular in attendance.

Besides this group of twenty-seven pregnant patients with manifestations of syphilis, there were five others who had been treated for early syphilis by the five-day method and subsequently became pregnant. Each one had attained seronegativity. Though they received no further antisyphilitic treatment during their pregnancies, five have already been delivered of normal infants, one case 20 months after completion of antisyphilitic treatment, another 17 months, a third 11 months, the fourth 3 months and the last 10 months later.

At birth serologic tests of the cord blood were made routinely. There were four cases in which positive reactions were obtained, three of which reverted to negative within a period of two months, the other requiring four months and all have remained negative during the several months that they have been followed. In twelve other cases the mothers' blood, although indicating a diminishing quantitative titre, still gave positive

reactions at the time of the birth while the cord blood of their infants gave negative reactions. One unusual situation arose in which a fetus received two courses of treatment while in utero with no ill effects. The mother had been treated for secondary syphilis when in her second month of pregnancy, and six months later, when in the eighth month of pregnancy, she received a second course of five-day treatment because of a serologic relapse. In each course of treatment the full dosage of 1,200 mg. of mapharsen was administered. The pregnancy terminated with the birth of a full-term, normal baby.

All of the eight patients with latent syphilis who received the massive dose treatment have been delivered of apparently normal infants. It is of interest to note that five of these women gave histories of previous pregnancies, in one instance of two, and the pregnancies of all had terminated in miscarriages or abortion. None of the patients with latent syphilis had received previous antisyphilitic treatment.

Thus it would seem that the efficacy of the five-day massive dose method of therapy for syphilis in pregnant women is attested to by the fact that normal infants were born in 25 of the 26 pregnancies. The one syphilitic infant was probably the result of a new infection acquired by the mother before the infant was born. The results were the same regardless of whether the mother had primary, secondary or early latent syphilis; and the stage of the pregnancy did not influence the outcome.

The results in this group of cases would seem to indicate also that the pregnancy had no special influence upon the course of the mothers' syphilis for the results from the massive treatment were similar to those obtained in nonpregnant persons. Of the twenty-seven cases, ten have already attained seronegativity; in nine cases serologic tests show the quantitative titre to be steadily decreasing; two cases resulted in serologic relapse, an incidence of about seven per cent thus far; and in two others there was evidence to suggest reinfection or superinfection. In four others, the trend of the serologic reaction cannot yet be determined. Of the eight patients with latent syphilis, two have attained seronegativity, one of them seven months after therapy, the other 11 months later. In one the serologic titre is steadily decreasing, and in the other five, the serologic reactions have thus far been unaffected.

The treatment-reactions observed in the pregnant women were similar to those observed in nonpregnant individuals. They consisted of slight fever, nausea, headache, pain in the arm and some dizziness. Transitory albuminuria was observed in about one-third of the cases. Numbness and tingling of the feet that was persistent to the point of being annoying developed in one patient. There were no cases, however, in which serious reactions occurred.

Summary

Twenty-seven pregnant women with syphilis were treated by the five-day massive dose method of chemotherapy. In the majority of these cases a modified technique was used in which both arsenic and bismuth were administered concurrently during the five-day period. The treatment was well tolerated by both mother and fetus regardless of the stage of the pregnancy or the duration of the syphilis, whether primary, secondary or latent. In no instance was there encountered a severe reaction or interference with the pregnancy.

Of the twenty-seven cases, one was lost from observation; twenty-five have resulted in the birth of full-term, normal infants; and one syphilitic infant was born of a mother who apparently had acquired a second infection while the infant was still in utero. In addition to this group, five other patients who had been treated for early syphilis by the massive dose method later became pregnant and gave birth to normally developed seronegative infants although further antisyphilitic treatment was purposely withheld from the mothers.

The results of the treatment upon the mothers' syphilis were similar to results obtained in nonpregnant patients treated by the same method for similar types of syphilis.

25 East Washington Street

Reference

1. Baehr, G., Leifer, W., Chargin, L., Hyman, H. T., Mahoney, J. F., Webster, B., Thomas, E., Sobotka, H., Mann, W. and Feldbau E.: Arch. Dermat. & Syph. 42: 239, 1940.

Discussion

DR. I. MICHAEL LEVIN.—I have observed twenty-six infants born of these women. Two were syphilitic and twenty-four were free of clinical, roentgenologic and serologic evidence of congenital syphilis. In the majority of instances the infants were hospitalized and weekly serologic studies were conducted for eight weeks and monthly thereafter.

One cause of confusion in the interpretation of the roentgen films was the presence of dense bands of calcification in the subepiphyseal zones. Dr. Rattner's remarks with reference to large doses of soluble bismuth being administered to the mothers may explain this picture.

On our service in the children's division of the Cook County Hospital, we have now treated about seventy-five infants with congenital syphilis by a method closely related to that described by the essayist. Radical changes in treatment had to be worked out because we were dealing with syphilis in a later and more widespread stage and with infants whose nutritional and growth requirements had to be met. Our experience with early acquired syphilis has been very successful and we are encouraged with our studies over the past three years with congenital syphilis.

The five-day treatment of early syphilis in pregnancy is entirely feasible, and offers the hope of a short, decisive control of syphilis, with the birth of normal children.

DR. BERTHA M. SHAFER.—In the survey made in Chicago, in 1937, we found that of 615 pregnant women who were infected with syphilis less than 50 per cent had been diagnosed as having syphilis before the fifth month of their pregnancy. We are agreed that if we are to have a good prognosis we must start our treatment before the fifth month. Not only must we start the treatment by that date, but we must carry on an intensive type of treatment with a high degree of regularity during the remainder of the pregnancy.

This evidently involves a hardship to many mothers, a fact proven quite conclusively by the observation that only 21 per cent of the women studied carried through with the treatment outlined for them. If the rapid five-day intensive treatment gives us better control over these patients, we should consider this point a definite advantage for this form of treatment.

Some believe that this rapid form of treatment does not sterilize open lesions very much more rapidly than two or three injections of arsphenamine might do.

It is true, if we compare the intensive form of treatment with the more conservative type, we cannot yet prove conclusively that we will not have more relapses. Syphilis has to be watched over a long period of time before we can speak of cure. Knowing they can be cured in five days may make these patients consider their infection is not too serious. I am sure we are going to have much difficulty in keeping a large percentage of these patients under observation long enough to prove the value of the treatment.

Let us consider the difficulties in enforcing completion of the older form of treatment. In the 1937 survey of the 11,400 patients that we studied, we found only 3,290 had had any previous treatment up to the time they came into the clinic. Since the disease was of more than four years' duration a little more than 72 per cent of these patients had suffered from it for four years without any treatment. Only 6 per cent of the women who had taken treatment had taken the minimal amount. Hence, you see how far from ideal were the conditions surrounding the other form of treatment.

My special interest in these pregnant women, concerns primarily the epidemiology of these cases. The results have been most revealing. The case of reinfection reported by Dr. Rattner is an outstanding example of the need of rendering all cases noninfectious. We know that her source of infection had been diagnosed as a primary case in August while she came into the hospital in November with secondary syphilis. The boy who was the source of the trouble did not follow through with the treatment, even though he had been urged to take intensive therapy at that time. In January, she had been made negative by treatment but she was then reinfected by this boy. We were also able to trace seven other primary and secondary cases which had resulted from this one case that had refused to have the intensive form of treatment. The epidemiology in syphilis is limited only by your time and energy.

THE USE OF VAGINAL TAMPONS FOR THE ABSORPTION OF MENSTRUAL DISCHARGES*

MADELINE J. THORNTON, M.D., MADISON, WIS.

(From the Department of Obstetrics and Gynecology, the University of Wisconsin Medical School)

DURING the recent years the use of vaginal tampons for the absorption of the menstrual discharges has increased greatly. Many patients using tampons for that purpose have inquired as to whether or not such a practice was harmful. Many gynecologists have expressed opinions on the subject, but there is little accurate information in the medical literature. This study was undertaken to determine if the use of self tamponage for the absorption of the menstrual discharges was harmful.

*This study was aided by a grant from the International Cellucotton Company, Chicago, Illinois.

Historical

The use of tampons in the vagina is not an innovation. In 1776, Leroux, a French physician in Paris, reported the use of vaginal tampons. He used a piece of tightly wound linen cloth dipped in vinegar, inserting it into the vagina to control hemorrhage and to treat leucorrhea. In 1806, Wendellstaedt, a German physician, used a tightly wound piece of linen cloth dipped in copper sulfate solution for the treatment of vaginal discharge and to stop hemorrhage. In 1888 Dührssen introduced the use of iodoform gauze as a tampon for vaginal antisepsis.

When packs of cotton, wool, gauze or rubber balloons are inserted into the vagina, nose, ear, or rectum, they are called tampons. Tampons of varying size, made of cotton or wool with a short string attached so that they may be removed from the vagina by the patient after a specified time, have been used by the medical profession since 1888 for the topical application of antiseptics or for the drying of the vagina. Long before our time theatrical performers and professional models used tampons in the vagina to absorb the menstrual discharges. The vagina was filled with absorbent cotton for this purpose.

On Sept. 12, 1933, a type of vaginal tampon for the absorption of the menstrual discharges was patented by E. C. Haas of Denver, Colorado, and, shortly thereafter, was sold by department and drug stores for that purpose. They became very popular about 1936 when an extensive advertising campaign was launched by the manufacturers. It was at about this same time that patients who were using these tampons began to ask physicians whether they were safe to use and whether the medical profession recommended their use. Since little, if anything, was known concerning the safety of their use, it was difficult to answer these questions intelligently.

Arnold and Hagele,[1] in 1938, reported an investigation which determined the efficiency of tampons in collecting the catamenial discharge of normal women. They suggested that, since tampons are foreign bodies in the vagina and since it is not known from experience how susceptible the vaginal mucosa might be to repeated irritation, periodic examination of the vagina should be made.

Much correspondence appeared in the *British Medical Journal*[2] in 1938 and 1939, some writers recommending the use of tampons and others condemning their use.

In 1939, Sackren[3] reported a study of 21 subjects who were observed over a period of three to five months' use of vaginal tampons for the absorption of the menstrual discharges. He concluded that the tampons used (1) offered complete protection to 90 per cent of the women observed and in 94 per cent of the menstrual periods studied; (2) showed no tendency to block the flow; (3) produced no observable changes in the vaginal or cervical tissues (no irritation); (4) caused no infections; (5) were easy and comfortable to use and eliminated odor; and (6) were favorably regarded by the patient.

In 1939, Genell and Lysander[4] reported three cases of colpitis which they attributed to the use of menstrual tampons. They regarded them as an unhygienic method of absorption of menstrual blood and did not recommend their employment as a substitute for perineal pads.

In 1939 a questionnaire was circulated among a group of American gynecologists asking them: (1) whether vaginal tampons furnished complete protection during the menstrual cycle; (2) whether vaginal tampons were free from all hazards of irritation, discomfort, introduction of infection, and arousing erotic tendencies; (3) whether tamponage prevented or eliminated menstrual odor. The majority of those who answered the questionnaire did not favor the use of vaginal tampons during the menstrual period, giving as reasons: (1) danger of infection, and (2) damming back of menstrual blood.

Since there was no accurate information available of studies carried on over any considerable period of time indicating whether or not the use of self-tamponage for the absorption of menstrual discharge was harmful, it was decided to undertake such a study.

Plan of Study

A group of 100 women between the ages of 19 years and 40 years volunteered as subjects for the study. They reported for an initial pelvic examination before starting the use of the tampons in November, 1939. At the time of this first examination a detailed menstrual history was obtained and the subject was instructed in the use of the tampon. Instructions to each subject were as follows: (1) Use the tampon throughout each menstrual period; (2) change the tampon at least every three hours during the time of the most profuse flow; and (3) observe carefully the following: (1) duration of the period; (2) are the tampons comfortable to insert; (3) are you conscious of the tampon while wearing it; (4) do you feel safe in wearing the tampon alone throughout each period; (5) does the tampon stay in place; (6) do you have any difficulty in removing the tampon; (7) is there any gush of blood following the removal of the tampon; (8) is there any vaginal discharge or any increase in vaginal discharge following the use of the tampon; (9) is there any pressure on the rectum or bladder by the tampon?

Tampons and vulvar pads to be used for each menstrual period were supplied to each subject throughout the period of study. Subjects were permitted free choice of one of five tampons which were available at the time this study was started. After the first examination each subject reported at intervals of every two months for an interview and a pelvic examination. All data obtained were recorded on special data cards. The study was completed in January, 1942.

The original plan had been to continue the study for a period of one year. As work progressed it seemed advisable to continue the observation over a longer period of time. Therefore, the study was extended over a period of another year, a total of 24 months.

From time to time during the two-year period subjects were lost from the group because of accepting employment in distant communities, illness, or pregnancy. At the end of the first year of study, eighty of

the original 100 subjects remained in the group to continue for another year. To this were added 23 new subjects. When the study was completed, 56 subjects had reported for 12 examinations, 30 subjects had reported for 6 examinations, and 24 subjects had reported for a varying number of examinations in excess of six (Table I). The 13 subjects who reported for less than 6 pelvic examinations; i.e., less than one year's period of observation have not been included in this analysis. Therefore, the observations which follow were made on 110 subjects who used vaginal tampons for the absorption of the menstrual discharge over a period of no less than twelve months and no longer than twenty-four months. During this period of time a pelvic examination was done on each subject every two months.

TABLE I

NUMBER OF SUBJECTS	MONTHS OF OBSERVATION	NUMBER OF EXAMINATIONS
56	24	12
6	22	11
8	20	10
3	18	9
4	16	8
3	14	7
30	12	6

Analysis of Results

All of the subjects were active young women between the ages of 19 and 40 years who were either students or career women; 14 members of the group were married and 96 members were single. Many in the group (63) had used vaginal tampons during menstrual periods for varying periods of time before becoming a member of this group. Forty-seven subjects had never used vaginal tampons before joining the group under study. Two members of the group had used tampons regularly for three years, two members had used them for two years, and the other 59 members of the group had been using them for times varying from one month to 18 months. It is interesting to note that one of the members of the group had used vaginal tamponage daily over a period of eighteen months because of leucorrheal discharge.

There was very little complaint of any discomfort experienced on introducing the tampon into the vagina. Twelve subjects stated that they had some discomfort on insertion of the tampon during the first menstrual period for which tampons were used. These were subjects who had never used tampons before. Those tampons encased in a cardboard tube were preferred by the subjects as they stated that they were more comfortable to insert.

The protection afforded by the use of the tampon was complete in 38 subjects, or 34.5 per cent. Protection was considered as complete only if the subject was able to use and felt quite safe in using the tampon alone without the additional protection of a vulval pad, throughout the entire menstrual period. Seventy-two of the subjects, or 65.5 per cent, found it necessary to use vulval pads in addition to the tampon during the period of maximum flow. Many of these subjects stated that they felt that the string attached to the tampon to facilitate its removal from the vagina acted as a "wick" thus making it necessary to wear a vulval pad for safety in protection.

Since this study was undertaken to determine, primarily, whether there were any harmful effects produced by the tampon, care was taken to record any pelvic pathology present at the time of the initial examination and to observe closely any change which occurred in this pathology during the period of observation. Throughout the study careful notation was made of any pathologic change which occurred. Vaginal smears and a hanging drop preparation of vaginal discharge were repeated at the time of the sixth, ninth, and twelfth pelvic examinations. It is to be regretted that these smears were not taken at the time of the first examination.

The one pathologic condition which was found most frequently was that of cervical erosion. Fifty-one of the 110 subjects showed some degree of cervical erosion. In 13 of these subjects the lesion was severe, extending over an area of approximately 1 cm. radiation from the external os, being very red and granular in appearance and having a tendency to bleed when wiped with a cotton pledget. Seven subjects had moderate cervical erosion in which the lesion extended for no more than 5 mm. radiation about the external os and did not bleed when wiped with a cotton pledget. Slight cervical erosion characterized by slight reddening and a granular appearance of the cervical mucosa extending 1 to 2 mm. about the external os was present in 31 subjects.

The other pathologic conditions occurred with much less frequency. Twenty-four subjects had a retroversion of the uterus. Three subjects had intramural fibromyomas of the uterus. Ovarian pathology was present in 17 subjects. Five subjects had a unilateral ovarian cyst present at the time of the first examination. Of the other 12 subjects with ovarian pathology, 9 had palpable enlargement of one ovary only and 3 had palpable enlargement of both ovaries. One subject had a cystocele and a rectocele. Fourteen subjects had a profuse purulent discharge, and 6 had a moderate purulent discharge present at the time of the first examination. This was invariably associated with the presence of a severe or moderate cervical erosion. A caseous discharge was present in 2 subjects. Twenty-five subjects had a moderate increase in the normal mucoid vaginal secretion.

Gynecologic surgery was done on three of the subjects who had a unilateral ovarian cyst because the patients were having symptoms which interfered with their performance of daily duties. Two of the subjects had a unilateral oophorectomy. The third subject had an oophorectomy and a supravaginal hysterectomy. No attempt was made during the period of observation of these subjects to correct cervical erosion or any pelvic pathology other than that described above. This was done deliberately so that one could evaluate more accurately any changes which might be caused by the tampon; i.e., increase in existing pathology.

At the conclusion of the period of study, i.e., twenty-four months after the first examination was made, 50 of the 110 subjects (or 45.5 per cent) showed no change in pelvic findings. In the 60 subjects in whom some changes were observed, the greatest change was in those of the 51 subjects in whom cervical erosion had been present at the initial examination. Fourteen had no cervical erosion and 17 showed less erosion at the end of the period of study. The cervical erosion was unchanged in the other 20 subjects. There was no increase in severity of the erosion in any case nor did any cervical erosion develop in a subject who had not had the lesion at her initial examination. Leucorrheal dis-

charge was less in the 20 subjects showing moderate to profuse purulent discharge. One subject, who had no increased leucorrheal discharge, had a moderate amount of mucoid discharge present at the end of the study. In one of the three subjects with fibromyoma uteri there was slight increase in the size of the tumor.

The incidence of infection with *Trichomonas vaginalis* and *Monilia albicans* was low in this group of subjects. Four subjects, or 3.63 per cent, had *Trichomonas vaginalis* organisms present in the vaginal secretion. Reported percentages of the incidence of *Trichomonas vaginalis* infection vary from 4 per cent to 69.9 per cent. Four subjects (3.63 per cent) had *Monilia albicans* present in the vaginal discharge. No other infections were present at the first examination or occurred during the period of study.

The following subjective information was obtained from the routine interrogation of each subject at the time of each examination: (1) 12 subjects reported some discomfort on inserting the tampon during the first menstrual period for which they used, (2) none of the subjects had any difficulty in removing the tampons, (3) 6 subjects noted a gush of blood following the removal of tampon on one occasion only; 2 subjects noted an occasional gush of blood following the removal of tampons. These subjects had a profuse menstrual flow; (4) 51 subjects noted an occasional increase in leucorrheal discharge; (5) 27 subjects noted occasional pressure on the rectum or bladder by the tampon (this occurring when the tampon had not been inserted high enough in the vaginal vault); (6) 92 subjects stated that they would continue to use tampons throughout the entire menstrual period, 11 subjects stated that they would use them during the last days of the period, only, when protection was complete; (7) one subject, only, stated that she felt that the use of the tampon caused an increase in dysmenorrhea. In no other instance did a subject state that the tampon had caused or had increased an existing dysmenorrhea; (8) 60 subjects stated that the use of the vaginal tampon had decreased or eliminated entirely the odor of the menstrual discharge. Twenty-six subjects stated that they had never noted any odor of the menstrual discharge.

Summary

One hundred and ten subjects using vaginal tampons for the absorption of the menstrual flow throughout each period were interviewed and examined every two months over periods of time varying from a minimum of one year (30 subjects) to a maximum of two years (56 subjects).

There was no evidence of any irritation of the cervix or vagina by the tampon.

There were 3.63 per cent of the subjects who had *Trichomonas vaginalis* organisms in the vaginal discharge. (This incidence of infection is lower than the average given in most statistical studies of groups of 100.)

There were 3.63 per cent of the subjects who had *Monilia albicans* present in the vaginal discharge.

No subjects acquired trichomonas or yeast infections during the period of study. There was no evidence of any other pelvic infection during this period.

There was no evidence that the use of the tampon caused obstruction to the menstrual flow.

Because of the greater comfort experienced, 103 subjects preferred to continue to use the tampons through part or all of the menstrual period rather than to return to the use of the perineal pad alone.

References

1. Arnold, L., and Hagele, M.: J. A. M. A. **110**: 790, 1938.
2. Correspondence, Brit. M. J. **2**: 1113, 1229, and 1282, 1938; **1**: 36, 1939; **2**: 143, 308, 1939.
3. Sackren, H. S.: Clin. Med. & Surg. **46**: 327, 1939.
4. Genell, S., and Lysander, A.: Svenska Läkartidningen, 2236, 1939.
5. Davis, C. H.: Curtis, Obstetrics and Gynecology **3**: p. 427.

EFFECT OF PREGNANCY ON THE MINERAL CONTENT OF DENTIN OF HUMAN TEETH*

MARTIN DEAKINS, D.D., AND JOHN LOOBY, D.D., BOSTON, MASS.
(From the Laboratory of Dental Medicine, Harvard School of Dental Medicine)

IT IS commonly believed that pregnant women have more dental caries than other individuals,[1] and that this supposed increase in caries during pregnancy is caused by demineralization of the teeth. The belief is that calcification of the fetus depletes the maternal stores of calcifying minerals to such an extent that even the mother's teeth are demineralized and hence are more susceptible to caries.

Clinical studies have shown that neither the extent of caries,[2] nor the incidence of new cavities,[2-4] is any greater in groups of pregnant women than in nonpregnant controls of the same age. Nevertheless pregnant women do have dental caries. If this caries is associated with metabolic demineralization of the teeth, one would expect the dentin to have a lower mineral content during the latter months of pregnancy than at other times. Although it has been concluded from clinical x-rays of the teeth in hyperparathyroidism that teeth do *not* take part in generalized decalcification,[5] no adequate chemical analyses can be found to support the idea that they may not be demineralized during pregnancy.

In order to test this possibility, the average mineral content of dentin from teeth extracted after the fifth month of gestation was compared with that of other teeth selected at random from nonpregnant subjects. Dentin was analyzed because it was felt that any change in the mineral content of this tissue would be greater than the relatively inert enamel. The method employed is based on the principle that the mineral content of enamel[6] or dentin[7] is proportional to its specific gravity. Specific gravity determinations were made on blocks of the noncarious portions of the dentin.

*Delivered at the University of Pennsylvania School of Dentistry, Philadelphia, Pennsylvania.

Experimental

Twenty-nine carious teeth, extracted from twenty patients during the latter months of pregnancy, were collected and preserved in 3 per cent formalin solution. Longitudinal sections were cut from them and ground planoparallel, approximately 0.5 millimeter in thickness. Blocks were then cut from the noncarious portions of the dentin and the specific gravity of each was determined by flotation in mixtures of bromoform and petroleum ether.

Results

Table I shows the average specific gravity of 152 samples of dentin from the pregnant group to be 2.12 with a range from 2.03 to 2.21. Apparently there is no progressive decrease in specific gravity from the fifth to the ninth month, either in the crown or root, as would be expected if decalcification were taking place.

Discussion

The use of specific gravity measurements as an index of calcification is justified by the high degree of correlation between the two.[6, 7] Also, comparison of carious teeth from this group with controls selected at random is allowable, for Black[9] has shown that the specific gravity of

TABLE I. SPECIFIC GRAVITY OF DENTIN IN CARIOUS HUMAN TEETH EXTRACTED DURING THE LATTER MONTHS OF PREGNANCY

AGE OF PATIENT	MONTH OF PREGNANCY WHEN TOOTH EXTRACTED	CORONAL DENTIN		ROOT DENTIN	
		NO. OF SAMPLES	AVE. SPECIFIC GRAVITY	NO. OF SAMPLES	AVE. SPECIFIC GRAVITY
20	V	2	2.18	4	2.10
13	V	2	2.21	1	2.07
19	VI	-	--	5	2.17
19	VI	-	--	4	2.10
16	VI	4	2.17	4	2.13
35	VI	-	--	3	2.05
35	VI	1	2.16	3	2.16
35	VI	4	2.16	3	2.18
?	VI	2	2.13	5	2.10
22	VI	3	2.13	2	2.12
22	VI	1	2.10	2	2.10
19	VII	-	--	6	2.11
19	VII	4	2.16	6	2.11
19	VII	1	2.03	1	2.08
17	VII	1	2.16	3	2.13
?	VII	3	2.09	5	2.08
16	VIII	5	2.13	1	2.11
19	VIII	-	--	4	2.08
19	VIII	1	2.14	2	2.09
19	VIII	5	2.12	4	2.09
20	VIII	3	2.09	3	2.09
20	VIII	2	2.15	4	2.13
16	IX	-	--	4	2.12
16	IX	1	2.04	1	2.06
21	IX	3	2.12	2	2.14
15	IX	1	2.10	3	2.12
20	XI*	3	2.11	4	2.08
?	?	-	--	6	2.09
?	?	2	2.14	3	2.15
Averages			2.13		2.11
Averages of all samples (152), 2.12					

*Extracted 6 weeks post partum.

the sound portion of dentin varies neither with sex nor the presence of caries.

The specific gravity of dentin from the pregnant subjects is not significantly different from that of the nonpregnant group[8] (Table II). Hence, it may be concluded that five to nine months of gestation withdrew no measurable amount of calcium salts from the dentin of these teeth. It is less probable that the relatively inert enamel was decalcified.

TABLE II. SPECIFIC GRAVITY OF DENTIN FROM PREGNANT AND NONPREGNANT WOMEN

	NO. OF TEETH	NO. OF DENTIN SAMPLES	AVE. SPECIFIC GRAVITY	RANGE OF SPECIFIC GRAVITY
Nonpregnant	14	40	2.08	1.82-2.22
Pregnant	29	152	2.12	2.03-2.21

No balance studies were made on these subjects, but the calcium intake, calculated from the institutional diets, was at most 1.6 Gm. per day. This amount of calcium may or may not have been adequate to maintain a positive calcium balance and also supply the fetal requirements.[10, 11] Whatever the state of the calcium balance may have been, active caries was present without a measurable loss of calcium salts from the teeth. Apparently, therefore, neither gestation, per se, nor demineralization of the teeth was associated with caries in this group of women.

Summary

No significant difference could be found between the average specific gravity (index of the degree of calcification) of dentin from pregnant women and from other individuals. The average specific gravity for dentin of the pregnant group was 2.12 while that of the nonpregnant controls was 2.08.

It was concluded that gestation did not cause a withdrawal of calcium salts from the dentin and, therefore, the caries already present in this group of pregnant women was not associated with a metabolic demineralization of that tissue.

We are indebted to The Division of Dental Research, University of Rochester, Rochester, New York, for the use of its laboratories in carrying out part of the work. We also wish to thank Dr. Percy Howe of the Forsyth Clinic, Boston, and St. Vincent's Hospital, Philadelphia, for collecting the teeth.

References

1. Klein, H.: Dental Cosmos **77**: 864, 1935.
2. Mull, J. W., Bill, A. H., and Kinney, F. M.: AM. J. OBST. & GYNEC. **27**: 679, 1934.
3. Ziskin, D. E.: AM. J. OBST. & GYNEC. **12**: 710, 1926.
4. Ziskin, D. E.: J. Dent. Res. **16**: 507, 1937.
5. Albright, F., Aub, J. C., and Bauer, W.: J. A. M. A. **102**: 1276, 1934.
6. Deakins, Martin: J. Dent. Res. **21**: 429, 1942.
7. Deakins, Martin: Proc. Soc. Exper. Biol. & Med. **46**: 62, 1941.
8. Deakins, Martin: Thesis, University of Rochester, Rochester, N. Y., 1940, p. 21.
9. Black, G. V.: Dental Cosmos **37**: 353, 1895.
10. Coons, C. M., and Blunt, K.: J. Biol. Chem. **86**: 1, 1930.
11. Macy, I. G., Hunscher, H. A., Nims, B., and McCosh, S. S.: J. Biol. Chem. **86**: 17, 1930.
12. Oberst, F. W., and Plass, E. D.: AM. J. OBST. & GYNEC. **40**: 399, 1940.

THE INFLUENCE OF THE PLACENTAL SITE UPON FETAL PRESENTATION

RICHARD TORPIN, M.D., AND L. P. HOLMES, M.D., AUGUSTA, GA.

(From the Department of Obstetrics and Gynecology and the Department of Roentgenology, University of Georgia, School of Medicine)

THE placenta acts as a foreign body of similar dimensions within the cavity of the uterus and has a tendency to displace the fetus, requiring the latter to conform to the remaining intrauterine space. It has been shown[1, 2] that the placenta usually occupies a discoid site comprising most of either the anterior or posterior wall. Snow and Powell,[3] in 1934, were probably among the first to note the site of the placenta as viewed by roentgen ray. They studied their patients by both anteroposterior and lateral views. In most of their cases the placenta appeared on one anterior or posterior wall, and thus appeared only in the lateral view. They stated that "in practically all of 60 cases the ventral part of the fetus faces the placenta. In no instance was the fetal back flush up against it. This appears to be natural because the placenta is very compressible and the relatively smooth back of the baby might disturb the placental circulation. Very often, a knee or elbow causes a pressure defect in it. When a part does abut on it, a line of increased density appears between. For the elbow, it is usually about 2 mm., for knees about 3 mm., and for the buttocks as much as 1 cm. It is our belief that this is caused by the greater penetrability by roentgen rays of the fat-containing subcutaneous tissues. Incidentally this finding is often helpful in locating the placenta."

Five years later in a second paper, Snow and Rosensohn[4] stated "in the diagnosis of the site of the placenta it was found that the structure could be seen in routine roentgen examinations of pregnancy in its late stages. The usual anteroposterior and lateral views were used but the lateral is more helpful. The placenta is seen as a soft tissue shadow which occupies about one-third of the wall space of the uterine cavity. It bulges in its middle where it measures about 7 cm. in diameter and tapers off at the periphery toward the uterine wall. The small parts of the fetus almost invariably face the placenta, and by pressure cause digitations in its substance. The subcutaneous tissues of the fetus, since they consist largely of fat, are highly penetrable by the roentgen rays and as a result, they leave a black line between the fetal parts and the placenta. For the elbow this may measure about 2 mm. and for the buttocks as much as 1 cm."

In the intervening years Dippel and Brown[5-7] further developed the method of visualization of the placenta in the x-ray film, using mainly

the lateral soft tissue view. They found the placenta visualized in 90 per cent of 262 observations by lateral soft tissue roentgenography. No errors were found in 53 cases checked by reliable clinical methods. They found equal division of anterior and posterior wall implantations.

Inasmuch as our technique of taking the films, developed independently over the past several years, coincides almost identically with that described by Dippel and Brown,[7] their paper is quoted: "The lateral film obtained by this method we believe to be the most important one in the study of the uterus and the product of gestation. Its correct interpretation requires not inconsiderable study and practice. If the film is properly taken, the posterior uterine wall may be clearly visualized with the aid of any viewing box, but the anterior abdominal and uterine walls which represent a much thinner area of tissue penetrated by the x-rays will be 'burned out,' i.e., over-exposed. However, by viewing those latter areas with a concentrated light, as with a 200-watt frosted bulb in an ordinary goose-neck lamp, with a shade, it can be as clearly made out as the posterior uterine wall and the latter's adjoining soft and osseous tissues."

Likewise their method of reading the films to bring out all of the meaning has been well stated by Dippel and Brown:[6] "The technic of viewing soft-tissue plates is quite important. This is certainly true of lateral views, as we have thus far been unsuccessful in obtaining lateral roentgenograms of even density. The intensity of different areas varies so widely that strong illumination, as with a spotlight, can be used to marked advantage in the region of the anterior abdominal wall. Since the exposure is made to produce the maximum soft-tissue detail in the region of the posterior uterine wall, the anterior uterine wall, which represents much less thickness of tissue, is over-exposed."

Carty[8] elaborated further: "The illumination with which soft tissue roentgenograms are viewed is of some importance. In all my cases, I like to use illumination of various colors, particularly green, red and blue, and often in this manner some soft tissue detail becomes apparent which otherwise might be lost. Also. I think it is of help to use a magnifying glass. Magnification methods depending upon projection of a certain portion of the film have not been successful, due probably to the relatively small difference in density of contiguous structures."

Material

In this study of 363 patients, practically all films were taken during the first stage of labor. We have found the value of the film to lie chiefly in its infallible ability to give the true presentation of the fetus, anteriorly and posteriorly. In addition, it gives the amount of engagement of the presenting part, the flexion of the head, the location of the placenta and some idea of the length of the true conjugate. The length of true conjugate and the diameter of the head are quite accurately obtained by applying to the midline of the abdominal wall a centimeter marked head rule which is usually done. A study is now in progress in regard to the measurement of the fetal head by this method compared to the actual measurement after delivery.

Furthermore, as brought out by Snow and his associates, and by Dippel and Brown, the lateral film is of marked aid in diagnosis in case of placenta previa and of premature separation of the normally implanted placenta.[9] Most of the results of this study of the influence of the placenta upon the position and presentation of the fetus are shown graphically in the chart.

Previously in almost all of the papers, such as those of Melhado,[10] Thoms,[11] Caldwell, Moloy, and D'Esopo,[12, 13] Cosgrove,[14] Calkins,[15] and D'Esopo,[16] on the subject of presentation, the main idea advanced was that the contour, shape, and size of the pelvis were the dominating features. Only now and then, as did Pennington, in a discussion of a paper on the subject,[15] did anyone suggest that the placenta might have considerable influence. Likewise, Melhado[10] stated that the placenta might be an etiologic factor, to wit: "May the true etiologic factor not lie in the uterus itself? With the placenta on the anterior wall, the child's back would more readily accommodate itself to the unoccupied posterior portion of the uterine cavity. This has frequently been proved by cesarean section."

TABLE I. SITE OF PLACENTA

PRESENTATION IN FIRST STAGE OF LABOR	ANTERIOR (163)		POSTERIOR (200)	
Occiput anterior	47	(29.5%)	117	(58.5%)
Occiput transverse	74	(44.7%)	60	(30.0%)
Occiput posterior	42	(25.8%)	23	(11.5%)

Fig. 1 reveals the following facts: there were a total of 363 cases, 176 white women and 187 colored women. (We excluded all breech cases, all indistinct films and those in which the placenta was not definitely outlined on either wall.) Among the white women, 80 placentas were located on the anterior and 96 on the posterior wall. In the colored women, 83 placentas were on the anterior and 104 on the posterior wall. Dippel and Brown noted equal distribution between the two walls. We, however, over a period of years, have made comment upon the fact that our series had more on the posterior wall, and we were of the opinion that 40 per cent were anterior and 60 per cent posterior. This study reduces the difference to 45 per cent and 55 per cent, but still it is seen to be appreciable and quite similar in the two races. For each year of study, the tallies were added in different colors and the ratios were found to be quite constant throughout.

From analysis of the figures noted in Fig. 1, it becomes apparent that in the 363 cases there were a total of 164 (45 per cent) occiput anterior presentations, 134 (37 per cent) occiput transverse presentations,* and 65 (18 per cent) occiput posterior presentations at the time of making the film in the first stage of labor. Still further analysis reveals that there were 163 cases with the placenta situated upon the anterior wall of the uterus. Among these, 47 (29.5 per cent) were associated with occiput anterior presentation of the fetus; 74 (44.7 per cent) with occiput transverse; and 42 (25.8 per cent) with occiput posterior presentation. On the other hand, 200 placentas were situated upon the posterior

*These are exact O.T. presentations. If they deviated more than five degrees, they became occiput anterior or occiput posterior.

CAUCASIAN WOMEN
PLACENTA POSTERIOR WALL 96
PLACENTA ANTERIOR WALL 80

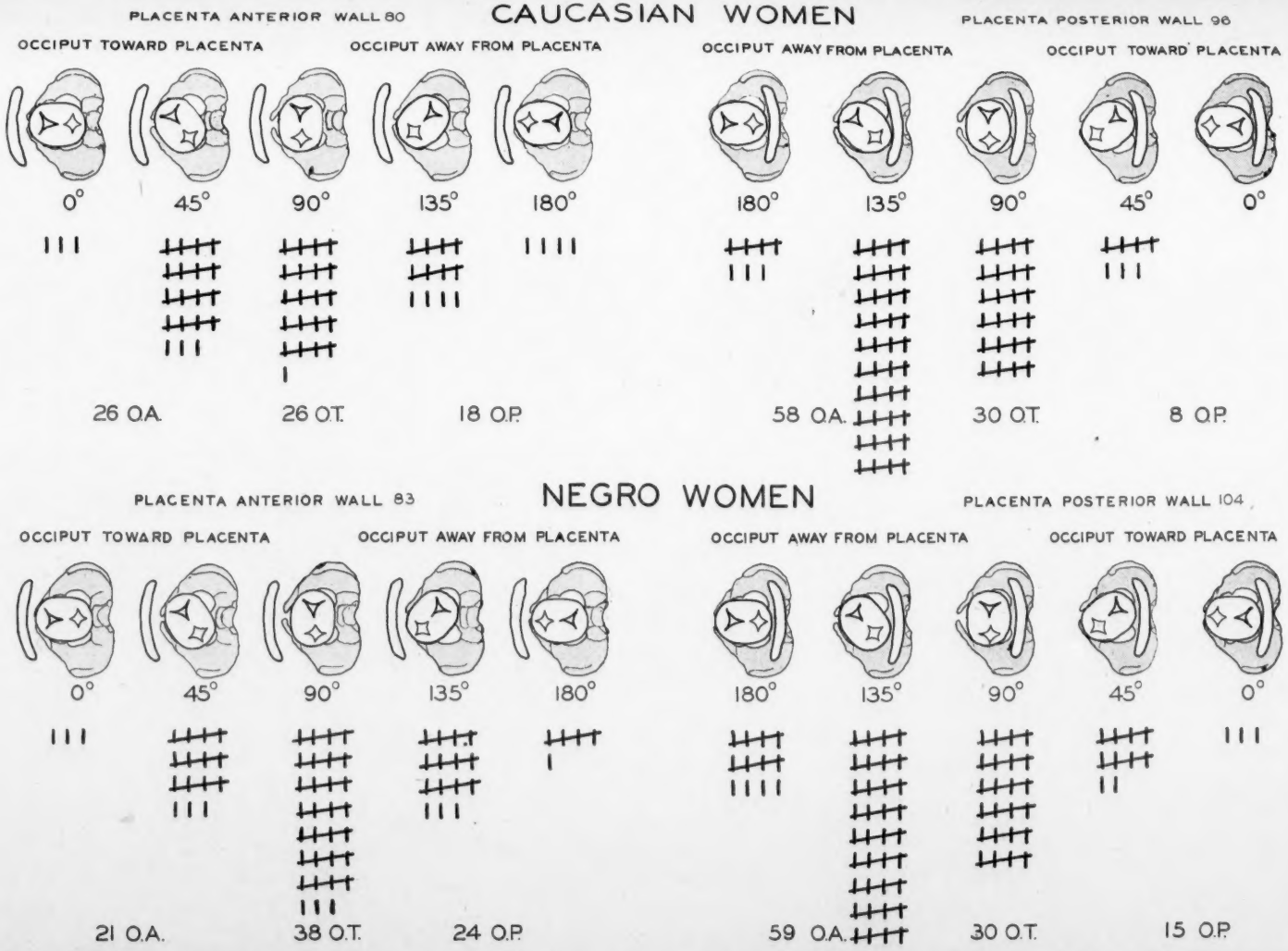

Fig. 1.—To the left of the midline the figures are represented with the placenta on the anterior uterine wall; to the right of the midline the placenta is represented as on the posterior uterine wall. The cephalic presentation is illustrated with the total number of such presentations tabulated below each figure. The placenta was on the anterior wall in 83 instances and on the posterior in 104.

wall in which the associated presentation of the fetus was 117 (58.5 per cent) occiput anterior, 60 (30 per cent) occiput transverse, and 23 (11.5 per cent) occiput posterior. Thus when the placenta was anterior, the incidence of occiput anterior presentations was only one-half what it was when the placenta was posterior, and when the placenta was anterior, the incidence of occiput posterior presentations was more than twice what it was when the placenta was posterior. Furthermore, occiput transverse presentation was 50 per cent more common when the placenta was anterior than when it was posterior.

Elsewhere,[2] it has been shown that the pregnant uterus is like an irregularly globular bag, wider at the fundus than its anterior posterior diameter. Now the cavity of this bag has been shown to have two essentially foreign bodies pressing into it either from one anterior or posterior wall, or into both; one of these is the bulky placenta and the other is the promontory of the maternal spine. Calkins[15] intimates that the full urinary bladder may also be a factor. The fetus, on the other hand, is essentially a parallelepiped with one concave ventral surface opposing a convex dorsal surface. Now when this geometric figure lies in the uterus, the great tendency is for the convex dorsum to lie opposite, or at least not toward the greatest indentation which is no doubt the promontory, after any degree of depression into the true pelvis has begun. However, the placental foreign body probably has a tendency to alter this position accentuating its effect, if it happens to lie on the same wall (the posterior) as the promontory, and a tendency to cancel the effect if it lies on the anterior wall. Of course, the shape of the pelvic inlet must have some effect upon presentation, a wide gynecoid inlet probably having a tendency to occiput transverse presentation, while a narrow anthropoid inlet quite certainly stimulates occiput anterior or occiput posterior presentation. In fact, that may well account for the main difference in this chart study between the white and colored patients. Occiput posterior presentation incidence is almost twice as high in Negro as in the white patients. It has been shown previously[17] that the Negro women have twice as great an incidence of anthropoid pelves as the Caucasians.

Conclusions

1. The great majority of placentas in human beings are located upon the anterior or the posterior wall of the uterus.

2. The ratio found in this study was 45 anterior to 55 posterior. These figures are exclusive of placentas of other sites which are relatively infrequent. This ratio was the same in both races studied.

3. The placenta located on the anterior uterine wall had a definite tendency to production of occiput posterior presenting fetuses. Mathematically when the placenta was anterior, the chance for occiput posterior presentation of the fetus was double what it was if the placenta was posterior (25.8 per cent to 11.5 per cent).

4. The placenta located on the posterior uterine wall had an increased tendency to produce occiput anterior presentations in the fetuses. In this case, when the placenta was on the posterior wall, the chance of the presentation being occiput anterior was twice what it was if the placenta was anterior (58.5 per cent to 29.5 per cent).

5. The incidence of occiput transverse presentation of the fetus in the first stage of labor was 30 per cent if the placenta was located on the posterior wall and 44.7 per cent if located on the anterior wall.

References

1. Holzapfel, K.: Beitr. z. Geburtsh. u. Gynäk. **1**: 286, 1898.
2. Torpin, Richard: J. Obst. & Gynaec. Brit. Emp. **45**: 993, 1939.
3. Snow, Wm. J., and Powell, C. B.: Am. J. Roentgenol. **31**: 37, 1934.
4. Snow, Wm. J., and Rosensohn, M.: Am. J. Roentgenol. **42**: 709, 1939.
5. Dippel, A. D., and Brown, W. H.: Am. J. Obst. & Gynec. **40**: 986, 1940.
6. Dippel, A. L., and Brown, W. H.: New England M. J. **223**: 313, 1940.
7. Dippel, A. L., and Brown, W. H.: Bull. Johns Hopkins Hosp. **66**: 90, 1940.
8. Carty, John R.: Am. J. Roentgenol. **42**: 717, 1939.
9. Torpin, Richard, and Holmes, L. P.: Bull. Univ. Hosp. Augusta, Ga. **3**: 10, 1941.
10. Melhado, G. C.: Am. J. Obst. & Gynec. **26**: 696, 1933.
11. Thoms, Herbert: Surg., Gynec. & Obst. **56**: 97, 1933.
12. Caldwell, W. E., Moloy, H. C., and D'Esopo, D. A.: Am. J. Obst. & Gynec. **28**: 824, 1934.
13. Caldwell, W. E., Moloy, H. C., and D'Esopo, D. A.: Am. J. Obst. & Gynec. **30**: 763, 1935.
14. Cosgrove, S. A.: Am. J. Obst. & Gynec. **31**: 402, 1936.
15. Calkins, L. A.: Am. J. Obst. & Gynec. **37**: 618, 1939.
16. D'Esopo, D. A.: Am. J. Obst. & Gynec. **42**: 937, 1941.
17. Torpin, Richard, and Homes, L. P.: Am. J. Obst. & Gynec. **38**: 594, 1939.

Ayre, J. E.: The Role of the Corpus Luteum in the Toxemia of Pregnancy, Canad. M. A. J. **44**: 575, 1941.

A possible explanation of the etiology of toxemia of pregnancy due to a disturbed endocrine balance, with the master gland of pregnancy, the corpus luteum, and the trophoblast of the placenta playing the major roles. Hypersecretion of these elements in toxemia produce an uncompensated endocrine imbalance and this has been advanced as the basic cause of excessive relaxation of all smooth muscle of the body (uterus, vascular system, bowel, ureters, etc.) which in turn lead to edema and other changes in organs of great vascularity, such as the liver, kidneys, uterus, and brain.

The use of vitamin B_1 as an antagonist to progesterone is suggested.

Carl P. Huber.

CAUDAL ANESTHESIA FOR CESAREAN SECTION

ALBERT H. LAHMANN, M.D., F.A.C.S., AND A. C. MIETUS, M.D.,
MILWAUKEE, WIS.

THE reintroduction of caudal block into our obstetric armamentarium once again demonstrates the cyclic trend so frequently seen in the course of medical progress. Medications, techniques, and the like, once popular, suddenly find themselves discarded only to be resurrected and accepted with renewed enthusiasm at some later date. So, too, with caudal block. Although extradural anesthesia, introduced via the sacral hiatus, has been utilized in obstetrics intermittently since the early part of this century, certain innovations have contributed to its recent popularity. To the availability of an anesthetic reagent of low toxicity yet of suitable efficacy can be attributed, in some part, the relative safety of the procedure. A technique devised for its continuous administration, as promulgated by Hingson and Edwards, throughout the course of the entire first, as well as the second, stages of labor has been made available. Furthermore, the service of caudal block has been extended to abdominal cesarean sections by taking advantage of the fact that the height to which the anesthetic solution dissects its way under pressure extradurally is directly proportional to the volume injected.

The scope of this paper embraces forty-eight cesarean sections performed under the single injection technique of caudal anesthesia. For the most part, forty-three cases, the series was derived from private practice; only five cases were obtained from the charity service of the Milwaukee County Hospital.

TABLE I. INDICATIONS FOR THE OPERATIONS

Previous cesarean	16
Cephalopelvic disproportion	12
Premature separation of the placenta	5
Toxemia without convulsions	4
Malpresentation	3
Placenta previa	2
Dystocia	2
Toxemia with convulsions	1
Previous extensive vaginal plastic	1
Previous stillbirth in an elderly primipara	1
Fetal distress	1

None of the sixteen women with whom previous section is listed as indication was permitted to fall into active labor. Although it is not our practice to routinely subject a woman to section because of a previous cesarean, it might be mentioned that none of this group had

ever in the past been delivered of a live baby *per vaginam*. On the other hand, all twelve of those listed under cephalopelvic disproportion were given the benefit of an adequate test of labor. The two listed under the ambiguous term, "dystocia," include instances where the cervix failed to efface and dilate and an attempt at delivery through the normal channels, even with the benefit of Dührssen's incisions, was not deemed advisable. Three stillborn infants were obtained where abruptio placenta occurred. In none of the five instances were premature separation of the placenta existed was extirpation of the uterus necessitated. The four toxemia-without-convulsion patients included one case of chronic glomerulonephritis and three of fulmonating pre-eclampsia where conservative measures were not availing. The single case of eclampsia was well controlled at the time of operation. The three instances of malpresentation include one transverse presentation and two cases, which we cite with due apologies under the heading of malpresentation, of large frank breech presentations where, after an ample trial of labor, section was resorted to in the interest of the infant. The woman in whom a previous vaginal plastic was considered as indication had undergone an anterior and posterior colpoperineorrhaphy and trachelorrhaphy. Both instances of placenta previa were of the complete type. In the one instance where fetal distress of undetermined etiology occurred, cesarean section was resorted to as the most rapid as well as the safest method, under the existing circumstances, of expediting delivery.

This series is comprised of forty-six laparotrachelotomies and two Porro cesareans. In no instance was a classical section performed. Three of the women were subjected to a Madlener sterilization.

The only postoperative complication worthy of note was a pelvic abscess which developed in a primipara subjected to a low cervical section after a protracted labor.

The anesthetic agent used for the series was a 2 per cent solution of metycaine (Gamma/2 methyl-piperidino/-propyl benzoate hydrochloride). There was some variation in the volumes injected. In two of the patients, 40 c.c. were injected; in four cases, 45 c.c. were used; in two instances, 50 c.c. were administered; and in the remaining forty, 60 c.c. of the metycaine were given.

All of the patients received a barbiturate preoperatively. Four of the series were given 3 grains of sodium amytal, while seven received 3 grains of pentobarbital; and the remaining received 4½ grains or more of pentobarbital. All but nine were given a preoperative hypodermic injection of atropine sulfate gr. $\frac{1}{150}$.

The lateral decubitus position of the patient at the time of injection was used with thirty-nine of the subjects; the knee-chest position with nine.

In three of the forty-eight cases, the block failed completely. That the cause for the failures is due to faulty technique on the part of the

operator is acknowledged. It must be assumed that a potent anesthetic agent, once instilled into the sacral canal, will anesthetize the nerves it bathes and that in those instances where anesthesia and analgesia fail to occur, the solution had, in all probability, never been properly introduced into the sacral canal. The complete failures were supplemented by inhalation anesthesia. In two instances the caudal block wore off before the operation was completed. Here, closure of the abdomen was affected under intravenous sodium pentothal. In one instance analgesia resulted but the anesthesia on the anteroabdominal wall failed to rise sufficiently high to permit an adequate incision. This patient's block was complemented by nitrous-ether anesthesia.

There were no maternal deaths in the series; none of the three fetal deaths could be attributed to the anesthetic or the type of its administration.

The development of satisfactory anesthesia is comparatively slow. The operator must expect to allot a latent period up to twenty minutes to transpire between the time of injection of the anesthetic to the time when an abdominal incision can be made without discomfort to the patient.

Untoward effects were occasionally witnessed. A sudden transitory fall in blood pressure was seen not infrequently, particularly in those instances where larger volumes of the anesthetic agent were instilled. In over half of the subjects a temporary slowing of the fetal pulse was noted for several minutes following the injection. In this series of forty-eight cases, the absence of such transient untoward reactions as jactitation, disorientation, hallucinations, etc., which we have witnessed at other times with caudal block, might be attributed to the preoperative administration of barbiturates. Whether purely coincidental or whether the barbiturates antidote toxic effects of metycaine is a matter of conjecture.

Invaluable for operative obstetrics, and particularly suited for cesarean sections, caudal block, not at all unlike spinal and inhalation anesthesia, defies promiscuous use and demands a certain degree of consideration and respect. That the procedure must be attended to with strict caution and assiduous regard cannot be overemphasized. An inadvertant intravenous or intrathecal, rather than extradural, injection will result in alarming reactions and may even terminate in a disastrous fatality. It is essential that scrupulous asepsis be observed in the technique lest pathogenic organisms be introduced into the areolar bed within the sacral canal, a fertile culture medium. Furthermore, not all women are suitable candidates for the procedure. Subjectively, the neurotic or apprehensive patient may vehemently object to even the suggestion of being permitted to remain conscious throughout her delivery. Objectively, in the obese woman with thick subcutaneous areolar sacral pads, identification of the bony landmarks may be so obscured as to make injection well nigh impossible.

In the appraisal of caudal anesthesia, what are the advantages of its use for cesarean sections? The paramount consideration of the obstetrician in attendance is, of course, the safety of the parturient and the welfare of her newborn. It befalls his oft-unhappy lot to decide not only on the indication for this type of surgical procedure—an operation of major importance with two lives involved—but he must recognize that the choice of anesthetic he will use will be as important as the surgical technique he will follow. He must appreciate that his patients are frequently seriously imperiled even before the cesarean is begun. The mother may be exhausted by the efforts of a prolonged labor; she may be shocked by the abrupt separation of her placenta; she may be exsanguinated by the hemorrhage of a previa; she may be ill with cardiovascular, renal or pulmonary disease. Similarly, the infant she bears may already have been subjected to the insult of a difficult labor, of embarrassed circulation, of toxemia, or of medullary depressants. Other matters to be considered are, that the infant is premature, perhaps barely viable; the mother is unprepared for an inhalation anesthetic; patients may vomit, with subsequent aspiration, atelectasis, pneumonia; ileus and other postoperative complications, any or all the price of a suprapubic delivery.

Caudal anesthesia then, is well suited for cesarean sections. A single injection of 60 c.c. of the anesthetic agent introduced into the sacral canal offers the laboring parturient relief from pain, relief from the attendant excitability, and produces abdominal anesthesia of ideal duration, of minimum length, yet consistent with efficiency and safety. The patient may be placed in the Trendelenburg position so that gravity displaces the unnecessary handling and packing of abdominal contents away from the operative field. Inasmuch as the uterus retains its tone, blood loss is minimal. The placenta separates without delay. The complete relaxation facilitates closure of the abdomen. The incidence of post-partum hemorrhage is diminished. The patient is comfortable on her return to bed and may be given fluids and food immediately after operation. Her puerperal convalescence is undisturbed and the subsequent involution of the pelvic organs is not influenced. The advantages over inhalation anesthesia are evident: there is no first-stage excitement, no vomiting, no danger of explosion; there is no irritating effect on the respiratory passages; no alteration in acid-base metabolism; nor any of the shock and dehydration which accompany prolonged inhalation anesthesia. The method can be used with comparative safety in patients with cardiovascular, pulmonary, or renal complications. Insofar as the infant is concerned, there is no immediate or remote hazard to its welfare which could be attributed to the anesthetic. In the elective cases, depression of the medullary centers is absent; the newborn's cry is spontaneous and lusty; in the emergency cases, asphyxia requiring resuscitation can, in all fairness, be attributed to the complications which demanded the cesarean rather than to the choice of anesthetic used.

Summary

The use of the single-injection technique of caudal block in a series of forty-eight cesarean sections is reviewed. That the method is not devoid of dangers is stressed. The precautions which must be exercised in its use are emphasized. The advantages and disadvantages of this type of anesthesia are discussed.

References

1. Lahmann, Albert H., and Mietus, A. C.: Surg., Gynec. & Obst. **74**: 63, 1942.
2. Hingson, Robert A., and Edwards, Waldo B.: J. A. M. A. **121**: 225, 1943.

AN ANALYSIS OF 250 CASES OF POSTMATURITY

LEWIS S. RATHBUN, M.D., BOSTON, MASS.

(From the Boston Lying-in Hospital and the Department of Obstetrics, Harvard Medical School)

THE subject of postmaturity is one about which very little has been written. The few papers about it have defined postmaturity, for the most part, in terms of the size of the infant. The problem of postmaturity in relation to the expected date of confinement is also important. The question continually arises as to whether or not the patient who is overdue should have labor induced. On the one hand, the obstetrician is faced with (1) a fretful patient who demands that she be delivered, (2) the fear of the ever increasing size of the baby, and (3) the fear, which is prevalent, that the baby may die in utero. On the other hand there is the feeling that the patient is doing very well and that it is meddlesome to interfere. It was in an attempt to find out just what happens to the postmature patient and her baby that this study was undertaken.

It is admittedly difficult to determine which patient is postmature. For this study a patient was considered postmature who was 295 days or more beyond the first day of her last menstrual period, or in other words, 15 days or more beyond her expected date of confinement. Any patient was excluded who was not sure of her last period or whose uterus at the time of her first clinic visit (usually at 4 to 6 months) was not consistent in size with her menstrual dates. In this manner it was hoped to eliminate as many who were not truly postmature as possible.

Material

A total of 3679 consecutive records was reviewed. Of these, there were 3289 deliveries of viable (28 weeks or over) babies. Postmaturity, as defined above, occurred 250 times. Thus, there was an incidence of 7.6 per cent, or 1 in every 13.2 deliveries. This figure agrees closely with the incidence of 7.3 per cent in 9649 cases reviewed by Clayton,[1] who used 294 days as his defining point. We see therefore that the problem arises rather frequently.

Of the postmature cases, 66 per cent were primiparas and 34 per cent multiparas. This is exactly the ratio of primiparas to multiparas in the total records studied.

There were four patients who exceeded their expected dates of confinement by 39, 42, 44 and 48 days respectively. The distribution of the other 246 cases appears in Figure 1, following a curve as might be expected. This curve may be superimposed almost exactly on the comparable portion of the curve of Hotelling[2] for the number of deliveries per day of pregnancy plotted for several thousand deliveries. The average time of delivery for the primiparas of my series was 19.4 days beyond the excepted date of confinement, while the multiparas averaged 20.2 days overdue.

The belief that postmature babies are heavier than term infants was found to be true in this series. The average weight of 600 term babies delivered during the period from which the postmature records were taken was 7 pounds, 3 ounces for the infants of primiparas, and 7 pounds, 10 ounces for the infants of multiparas. The average weight of the postmature babies of primiparas was 7 pounds, 12 ounces, a gain of 9 ounces. The postmature infants of multiparas averaged 10 ounces more than the term babies, or 8 pounds, 4 ounces. Since this involves a series of fairly large numbers, there can be little doubt as to the validity of the figures.

In an attempt to break down further the figures on the weights of the babies, the weights of the postmature infants were averaged in two groups. One group consisted of those delivering between 15 and 19 days postmaturely, and the other group of those delivering 20 days or more after their expected date of confinement. Surprisingly, the infants of primiparas in the first group averaged 7 pounds, 13½ ounces, while those who were 20 or more days postmature averaged only 7 pounds, 9⅓ ounces. The infants of multiparas showed the earlier group to be about 1 ounce heavier, averaging 8 pounds, 4⅓ ounces, in contrast to 8 pounds, 3½ ounces for the more postmature group.

This apparent loss of weight in the later days of postmaturity is difficult to explain. It may be that splitting the series up into smaller groups has invalidated the figures. It may also mean that after a certain time the aging placenta ceases to nourish the fetus as well as formerly, stopping development and causing the fetus to begin to live off of its stored resources. However, the marked gain in weight shown by the group as a whole seems to indicate clearly that the postmature mother is faced with the problem of delivering a larger fetus than she would have delivered at term.

The fact that the babies are larger leads one to surmise that labor would be longer in the postmature group. The average length of labor for 500 mothers at term who delivered in the same months and with the same analgesia as the postmature mothers was 14.9 hours for primiparas and 8.8 hours for multiparas. The postmature primiparas were in labor an average of 18.2 hours, while the multiparas were in labor 10.5 hours. Thus, the postmature primiparas were 3.3 hours longer in labor, while the multiparas required 1.7 hours longer.

One might also surmise that operative intervention would rise with the increase of weight of the fetus and the length of labor. This was the case. The number of operative deliveries, excluding breeches (of which there were 6), rose from a clinic percentage for the period of 24.4 per cent to 30.8 per cent, or an increase of 6.4 per cent.

When the operative figures are broken down, we find a marked increase in the more serious types of operations. There were 5 midforceps in the 250 postmature cases. This is far above the usual clinic ratio, as midforceps are rarely done. There were three Waters' extraperitoneal cesarean sections done. This again is a much higher ratio than the clinic ordinarily runs. The numbers of low forceps and transperitoneal cesareans were not increased remarkably.

The morbidity might be expected to rise because of the aforementioned conditions. The increase was marked. The postmature patients had a morbidity of 12.4 per cent, against a clinic morbidity for the same period of 4.7 per cent. Retention of lochia, cystitis and intrauterine infection, in that order, accounted for most of the morbidity.

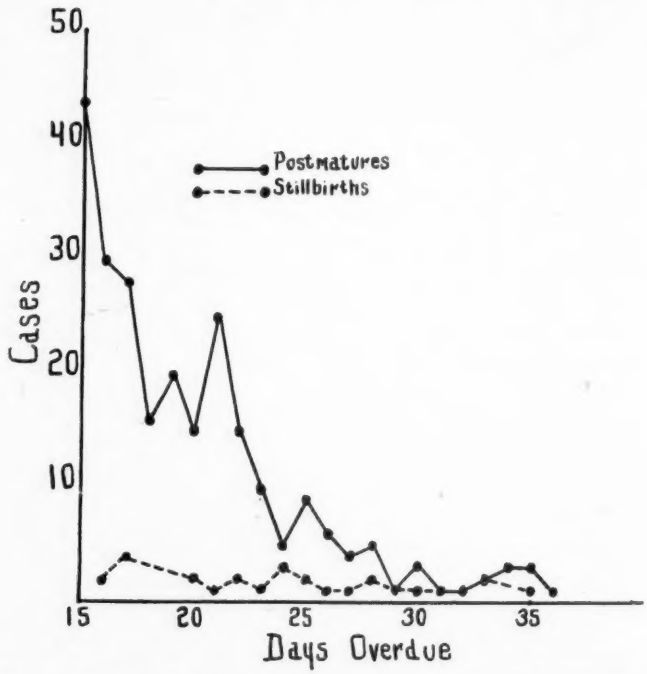

Fig. 1.—Showing distribution of postmature infants and stillbirths.

There is a definite belief among obstetricians that postmature infants tend to die in utero. Consequently, considerable time was spent in studying the stillbirths in this series and a series of consecutive clinic stillbirths. There were 13 stillbirths in 250 postmature births, or 5.2 per cent. Clayton[1] found a stillbirth rate of 6.5 per cent in his postmature series. The clinic stillbirth rate for viable (28 weeks or over) infants over the 1½ years covered by this paper was 2.5 per cent. However, 43 per cent of these were due to prematurity. For comparison with the postmature group, it seems fair to disregard the prematures, as obviously none of the postmature died of prematurity. So we find a term stillbirth rate in the clinic of 1.4 per cent, compared to a rate of 5.2 per cent for the postmatures.

The distribution of postmature stillbirths does not follow the curve of distribution of cases in Fig. 1. Stillbirths were scattered evenly throughout the postmature period. The average number of days post-

mature was 24.4 per cent, or somewhat longer than the average for living infants.

In an attempt to ascertain the cause of the increased stillbirths, a separate series of 186 consecutive stillbirths, including the 13 postmatures already mentioned, was studied. Of these 27, or 1 case in 6.9, were postmature, substantiating the feeling that stillbirths were increased in postmaturity, since 1 in 13.2 normal cases was postmature. Prematurity accounted for 84 cases of stillbirths.

The term and postmature stillbirths were separated, and each group was then divided into a subgroup of those dying before or during labor. Each subgroup was then divided into those for which a cause of death could be determined and those for which no cause could be ascertained. Cause of death during labor embraced many things such as prolapsed cord, difficult forceps or breech delivery, destructive operations for hydrocephalus, etc. Causes of death before labor were erythroblastosis, pneumonia in the mother, and the cord wound tightly about the neck. Of course, it can not be proved that the last was the cause of death, but it was noted as such in the record. Table I shows the number and percentage of cases in each group.

TABLE I

	MATURE		POSTMATURE	
DEATHS	NUMBER	PER CENT	NUMBER	PER CENT
Before labor				
No cause	12	16.0	5	18.5
Cause apparent	7	9.3	5	18.5
During labor				
No cause	7	9.3	3	11.1
Cause apparent	49	65.6	14	51.9

The series is too small to expect perfect agreement of the percentages in Table I. It would seem to be clear from these figures that there is no great difference between the cause of death in the mature and postmature stillbirths. Certainly there would seem to be no increase in the number of babies who died for no apparent cause, which is what popular opinion would lead us to believe. Clayton[1] also concluded that there was no increase in stillbirths without evident cause in postmaturity. The only difference which might be important is the difference of those dying before labor where the cause was apparent. This was caused by the appearance of the same number of erythroblastotic stillborns (3) in each series despite the larger series of term infants.

It should be noted that there were no stillbirths in the postmature group from premature separation of the placenta. One might think that premature separation of the placenta might be a frequent cause if degeneration of the placenta took place. The age of the mothers of stillborn infants did not vary from the average age of the series mothers.

Although the series is small and consequently the figures open to question, it would seem that postmature infants are no more inclined to die for no apparent reason than term infants. It can not be denied that there seems to be a tendency for the postmature infant to succumb more easily than the mature to the various trials that beset him, or because he is bigger and better developed the trials are more strenuous.

It is interesting to note that study of a large number of postmature placentas led Reynolds[3] and Masters and Clayton[4] to conclude that

postmature placentas showed no increase in degeneration over mature placentas. This gives added weight to the thesis that infants do not die of postmaturity alone.

There were 2 neonatal deaths in the 250 cases. One was caused by diaphragmatic hernia and one by erythroblastosis. A study of the living infants' post-partum-weight charts showed no striking difference from those of the term infants.

There was one maternal death. The patient died of hemorrhage and shock following a long labor terminated by Waters' extraperitoneal cesarean section. So we see that increased difficulty in labor is not without danger to the mother as well as to the child.

Conclusions

A series of 250 carefully selected, consecutive cases of mothers who delivered at least 15 days beyond their calculated date of confinement was studied, together with an additional series of 186 consecutive stillbirths. Postmaturity occurred once in 13.2 deliveries. Postmature infants were significantly heavier than term babies at birth. However, they seem to lose the tendency to gain after they are 20 days postmature. Coincident with the increase in weight is an increase in the length of labor; an increase in the operative rate, especially in the more serious operations; and a marked increase in morbidity.

The stillbirth rate was definitely increased. This was an increase in the deaths with apparent cause rather than in deaths where there was no cause except postmaturity. The stillbirths were longer postmature on the average than the general series, averaging 24.4 days beyond term as against 19.6 days for the 250 patients.

The babies who were born alive showed no increase in neonatal deaths nor any difficulty in the post-partum period.

The question as to what to do about postmaturity has not been answered. The increase of difficulty found in postmature patients is not of sufficient magnitude to warrant drastic measures to keep patients from becoming postmature.

The answer to the problem probably lies in the realization that it exists. Each case should be watched individually. If the cervix is favorable, induction of labor is indicated. If it is not, then the size of the fetus must be carefully evaluated against the size of the mother's pelvis, and a close watch must be kept on the increasing size of the fetus. No more fear need be entertained that the fetus will be lost in utero without cause than exists at term. However, failure to appreciate the fact that labor may be more difficult and to prepare to meet these difficulties may cost the baby its life or even the mother hers.

References

1. Clayton, S. G.: J. Obst. & Gynaec. Brit. Emp. **48**: 450, 1941.
2. Hotelling, H., and Hotelling, F.: Am. J. Obst. & Gynec. **23**: 643, 1932.
3. Reynolds, F. N.: Proc. Roy. Soc. Med. **31**: 781, 1938.
4. Masters, M. I., and Clayton, S. G.: J. Obst. & Gynec. Brit. Emp. **47**: 437, 1940.

221 Longwood Ave.

CLINICAL EXPERIENCES WITH PYRIDOXINE HYDROCHLORIDE IN TREATMENT OF NAUSEA AND VOMITING OF PREGNANCY

B. Bernard Weinstein, M.D., George J. Mitchell, M.D., and George F. Sustendal, M.D., New Orleans, La.

(From the Departments of Obstetrics and Gynecology, School of Medicine, Tulane University and Charity Hospital of Louisiana)

VOMITING is always an annoying and not infrequently a serious complication of pregnancy. Numerous methods have been advocated for its relief without any uniform degree of success. For some time we have used mild sedation (phenobarbital), restriction of fluid intake and Vitamin B_1 in the milder cases, and sedation, bed rest, plus intravenous glucose in the more severe cases, with considerable success; however there were still many instances where this regime was only partially successful or failed. Recently our attention was directed to an article of Willis and his co-workers, who reported the successful use of Vitamin B_6 in hyperemesis gravidarum. A supply of pyridoxine hydrochloride* being made available, we first used this therapy upon a patient who had been treated with other methods without success. The results were so good that we introduced the use of the drug as a method of routine and have now used it in 32 patients. We will continue to use it on a more extended series of cases.

In studying these patients an attempt was made to grade the severity of nausea and vomiting in order to express with some degree of uniformity the degree of nausea and vomiting present: Morning nausea was considered (1+) Group 1; nausea extending throughout the day (2+) Group 2; nausea and occasional vomiting (3+) Group 3; nausea and vomiting of a degree prohibiting the retention of any fluids or solids (4+) Group 4. While most of our patients fall into Group 1, the response of patients to therapy was seemingly not dependent upon the severity of nausea and vomiting present since several patients of Group 4 responded as readily as those of Group 1.

In all cases an initial dose of 50 or 100 mg. was administered intramuscularly, followed by injections of 50 to 100 mg. three times weekly until nausea subsided. Some patients reported favorable response with the first injection. In the most severe cases relief was not attained until the third or fourth injection. The largest amount given to any one patient was 1,050 mg.

Discussion

We were gratified by the rapid response to therapy. There were no untoward reactions to the drug. While the dosage we used was considerably larger in general than that employed by Willis and his associates, it is probable that smaller dosage would give equally good results.

All of these patients were treated with intramuscular injections. Since this series was started pyridoxine hydrochloride has been made available in tablet form, and we are currently observing a group of pa-

*Pyridoxine hydrochloride was supplied through the courtesy of the Winthrop Chemical Company.

tients who are being treated by oral administration of pyridoxine hydrochloride.

The results obtained in the patients of Group 1 are not remarkable since most of the patients probably would have responded to other types of therapy; however the rapidity of relief is noteworthy. The response in the more severe types, and especially in the Group 4 is more striking. This type of patient who has not infrequently required hospitalization may be effectively and economically treated with pyridoxine hydrochloride at home.

While the administration of pyridoxine hydrochloride appears to be of great value we feel that the importance of sedation and proper instruction as to diet should not be overlooked, but should be prescribed as usual, with pyridoxine hydrochloride as a valuable adjunct in the therapy of nausea and vomiting of pregnancy.

Conclusions

1. Complete or considerable relief from nausea and vomiting of pregnancy was obtained in a group of 32 patients who were treated with pyridoxine hydrochloride in dosages of 50 to 100 mg. three times weekly, receiving total dosages varying from 150 to 1,050 mg. injected intramuscularly.

TABLE I. GROUP I. (GRADED AS 1+, MORNING NAUSEA ONLY)

PATIENT	DOSAGE	TOTAL DOSAGE MG.	RESULTS
L. K.	50 mg. I,* 50 mg. 3 t.i.w.	150	Good
C. S.	50 mg. I, 50 mg. 3 t.i.w.	250	Good
P. L.	50 mg. I, 50 mg. 3 t.i.w.	150	Good
R. T.	50 mg. I, 50 mg. 3 t.i.w.	300	Good
M. E.	50 mg. I, 50 mg. 3 t.i.w.	400	Good
M. K.	100 mg. I, 50 mg. t.i.w.	300	Good
E. V.	50 mg. I, 50 mg. t.i.w.	500	Nausea still occurs, though less often
M. N.	50 mg. I, 50 mg. t.i.w.	450	Good
H. P.		150	Good
J. G.		200	Good
A. R.		350	Good
P. W.	100 mg. I, 50 mg. t.i.w.	450	Poor, nausea occasionally, but not as severe. (Patient was incidentally markedly anemic)
E. Y.	50 mg. I, 50 mg. t.i.w.	200	Good
F. C.	50 mg. I, 50 mg. t.i.w.	200	Good
R. E.	50 mg. I, 50 mg. t.i.w.	250	Good
L. C.	50 mg. I, 50 mg. t.i.w.	300	Good

*I = Initial dose.

TABLE II. GROUP II. (GRADED AS 2+, NAUSEA EXTENDING THROUGHOUT DAY)

PATIENT	DOSE	TOTAL DOSAGE MG.	RESULT
E. S.	50 mg. I,* 50 mg. t.i.w.	400	Good
R. P.	100 mg. I, 50 mg. t.i.w.	450	Good
H. T.	100 mg. I, 50 mg. t.i.w.	350	Good
L. P.	50 mg. I, 50 mg. t.i.w.	400	Good
A. D.	50 mg. I, 50 mg. t.i.w.	600	Good
P. J.	50 mg. I, 50 mg. t.i.w.	650	Good

*I = Initial dose.

2. Of the 16 patients with nausea confined to the morning 14 were completely relieved; 2 were partially relieved (Table I). Of the 6 patients with nausea extending throughout the day all were completely relieved (Table II). Of the 4 patients having nausea and occasional vomiting 3 were completely relieved; the fourth showed but slight improvement (Table III).

TABLE III. GROUP III. (GRADED AS 3+, NAUSEA AND OCCASIONAL VOMITING)

PATIENT	DOSE	TOTAL DOSAGE MG.	RESULT
L. D.	100 mg. I,* 50 mg. t.i.w.	700	Good
F. S.	100 mg. I, 50 mg. t.i.w.	750	Good
R. L.	100 mg. I, 50 mg. t.i.w.	600	Good
M. Q.	100 mg. I, 50 mg. t.i.w.	900	Poor, nausea persisted; patient vomited less after 250 mg. but never received complete relief.

*I = Initial dose.

All of the six patients with nausea and vomiting so severe as to make impossible the retention of food were relieved. This group showed the most striking and gratifying response (Table IV).

TABLE IV. (GRADED AS 4+, NAUSEA AND VOMITING SUFFICIENTLY SEVERE TO PREVENT RETENTION OF ANY FOOD)

PATIENT	DOSE	TOTAL DOSAGE MG.	RESULT
M. J.	100 mg. I,* 100 mg. t.i.w.	600	Good
D. G.	100 mg. I, 100 mg. t.i.w. x3, 50 mg. t.i.w.	750	Good
M. P.	100 mg. I, 50 mg. t.i.w.	1050	Good
H. B.	100 mg. I, x4, 50 mg. t.i.w.	850	Good
R. C.	100 mg. I, 50 mg. t.i.w.	600	Good
D. E.	100 mg. I, x3, 100 mg. t.i.w.	900	Good

*I = Initial dose.

3. No untoward effects were noted.

4. While the use of pyridoxine hydrochloride has proved of value in these 32 patients, the importance of sedation and adequate dietary supervision should not be overlooked, but should be prescribed as usual with pyridoxine hydrochloride used as an integral and valuable portion of this regimen.

5. Our series is being extended and observations are also being made with the use of orally administered pyridoxine hydrochloride.

Reference

Willis, R. S., Winn, W. W., Morris, A. T., Newsom, A. A., and Massey, W. E.: AM. J. OBST. & GYNEC. 44: 265, 1942.

1430 TULANE AVE.

CARCINOMA OF THE VULVA AND VAGINA IN INFANCY

RANDOLPH H. HOGE, M.D., F.A.C.S., RICHMOND, VA., AND
VERNARD A. BENN, M.D., ROSHOLT, WIS.

(From the Departments of Gynecology and Pediatrics, Medical College of Virginia)

CARCINOMA of either the vulva or vagina is very rare in infancy. Ritvo, Houghton, and McDonald,[1] Scotti,[2] Kellert,[3] and Dargeon,[4] writing on the subject of malignant tumors in childhood, report no cases of carcinoma of the vagina or vulva. Ewing[5] points out that the tumors occurring during the first decade of life are those likely to be characteristic of the juvenile types of tumors. Malignant epithelial tumors represent a small minority of those occurring during this period of life.

Morse,[6] upon reviewing the literature, states that carcinoma of any part of the female genital tract is rare in childhood. In his review he found only two instances of malignant epithelial growths of the external female genitals in children. The growth in one case originated in the vulva. The other case was that of an eight-month-old child in whom an adenocarcinoma extended from the wall of the vagina to the anterior cervical lip.

Kelly,[7] in a paper on cancer in children, reports that gynecologic cancer is seldom encountered in children. He reports no case of carcinoma of the vulva or vagina in infants, except to refer to the vulvar case previously referred to by Morse and noted above.

In 1931 Baldwin[8] reviewed 905 cases of carcinoma of the uterus, vagina, and vulva occurring at the University of Michigan. The youngest patient in his series was a girl of fourteen years who had a primary carcinoma of the vagina. He searched the literature for cases occurring in patients twenty years old or younger. Concerning the vagina he found only one case in a child. This case was reported by Heckford[9] in 1868. The growth was said to be a villous medullary carcinoma protruding from and distending the vagina of a child ten months old. Heckford's article has not been available to us. Baldwin found no definite case of carcinoma of the vulva in an infant. Reference was made to a vulvar tumor occurring in a child of eighteen months, reported by Bietrix and by Thomas,[10] but the latter originally described the growth as a sarcoma.

Lövegren[11] reports the case of a malignant papillary epithelial tumor of the vagina occurring in a child of seventeen months of age. Symptoms had been present only three weeks. Three months later the growth had extended to the vulva, and the patient died six months after the onset of the disease.

The rarity of malignant epithelial tumors of the vagina and vulva in infancy might lend interest to the following case:

Case Report

D. J. was a full-term child, the product of a normal spontaneous delivery on June 6, 1934. Her maternal grandmother died with cancer of the stomach. Her father and mother and six siblings were alive. The father was said to have pulmonary tuberculosis.

She had had no illnesses until she was five months old. At that age she developed a purulent blood-streaked vaginal discharge. For the following ten months there was little change in the character of the discharge. None of the various treatments which she received was effective. She became sallow and lost weight. In October, 1935, when

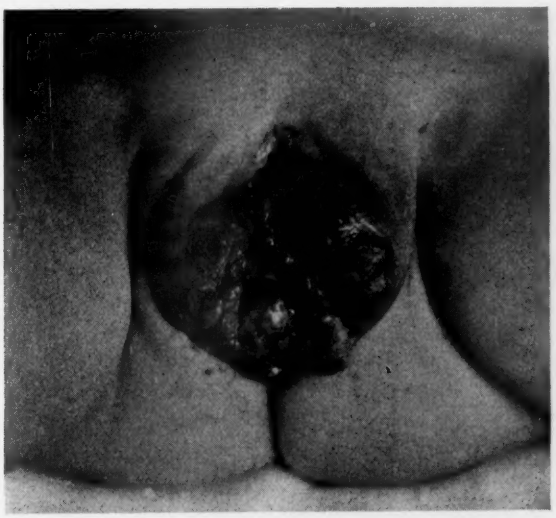

Fig. 1.—Adenocarcinoma of vulva before treatment. Patient was 21 months old.

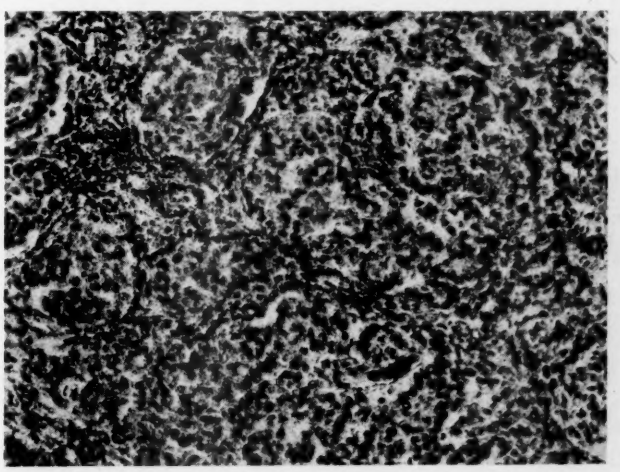

Fig. 2.—Photomicrograph of frozen section of lesion seen in Fig 1. Diagnosed adenocarcinoma, Grade IV.

she was sixteen months old, a swelling appeared on the right labium which ruptured and discharged blood and pus. One month later a similar swelling appeared on the left side. This likewise ruptured and drained pus. During the succeeding months the lesion enlarged. It was described as "proud flesh" and was not remarkably painful.

She was first seen by us on admission to the Hospital in March, 1936, when she was twenty-one months old. At that time there was a very friable, easily bleeding, cauliflower mass, somewhat spherical in shape with a diameter of 5 cm. The center of the growth was at the lower portion of the introitus near the posterior commissure. The growth extended into the labia on each side, further on the left. The sites of the ducts of Bartholin's glands were included in the mass. The mass extended into the vagina for a distance of about 2.5 cm. above the introitus, involving the posterior and lateral walls of the vagina. The anterior wall was free. The cervix was not involved. Some areas of the tumor were so soft that semisolid tissue exuded on pressure. Smaller areas were harder. In the left side of the pelvis, and palpable through the vagina, there was a firm, bean-shaped, movable mass about 1 cm. in length, believed to be an enlarged iliac lymph gland. Smaller shotty glands were palpable in each inguinal region. Tissue was re-

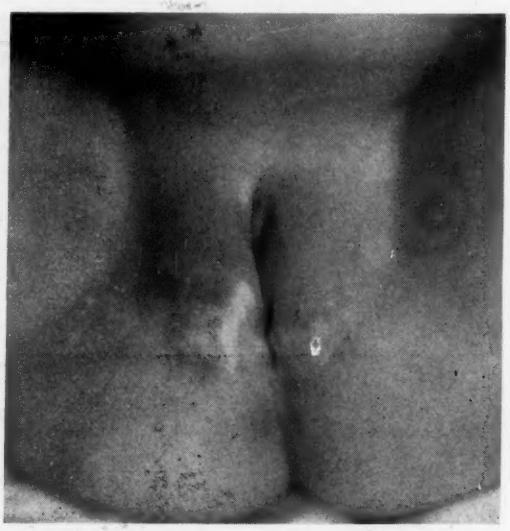

Fig. 3.—Same patient as in Fig. 1, two months later and after irradiation.

moved for microscopic examination. Dr. A. C. Broders, who examined the tissue, reported adenocarcinoma, Grade 4. A small lymph gland was excised from the left inguinal region and a pathologic report of tuberculous adenitis was made.

On April 4, 1936, treatment with radium was begun. Twenty-nine 1.0 mg. needles, with a filtration of 0.5 mm. of platinum, were applied to the growth interstitially. This treatment extended over a period of four days and a dose of 2,374 mg. hr. was given. There was marked regression of the lesion during this time. Between April 17, 1936, and July 7, 1936, the patient was given deep x-ray therapy to the pelvis, totaling 4,200 r. Two months after the beginning of treatment there was no evidence of the growth. She was discharged from the hospital on July 27, 1936.

The patient returned to the hospital in October, 1936, several months after the treatment with radium. At this time there was a small area of recurrence, measuring slightly over a square centimeter, on the posterior vaginal wall, midway between the introitus and the cervix.

This area was treated with interstitial radium, a total of 133 mg. hr. being given. This radium treatment was followed by further x-ray treatment, 2,400 r. being given. The mass previously palpated deep in the left side of the pelvis had increased in size. Following the second series of treatments the patient developed a painful area of radionecrosis about the vulva and lower vagina. This condition was improving when she was discharged from the hospital on Feb. 9, 1937, with chickenpox.

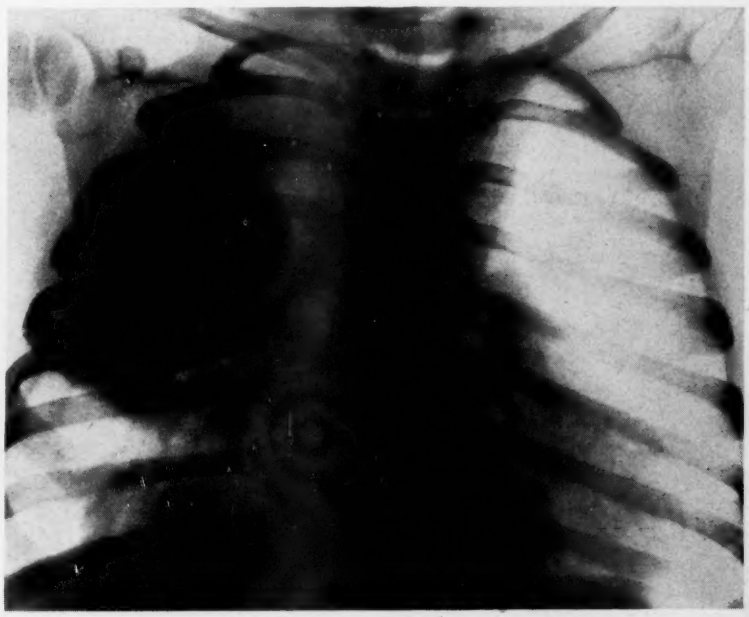

Fig. 4.—X-ray of chest, one year after Fig. 1, showing metastasis.

On March 26, 1937, she returned to the hospital acutely ill. The area of necrosis was smaller. No carcinoma was apparent on the vulva or in the vagina. The left leg was swollen and cyanotic throughout. It appeared several times as large as the right leg. Her temperature was 104° F.; her respirations and pulse were very rapid. X-ray examination of the chest at that time showed an oval density practically filling the upper two-thirds of the right lung. This was diagnosed metastatic carcinoma. X-ray therapy was given. The enlargement of the left lower extremity was believed to be due to obstruction by the mass deep in the left side of the pelvis. The patient continued to be very weak and seemed to suffer pain. She developed a cough and dilatation of the veins of the head and neck. Her condition continued to progress unfavorably and she was discharged from the hospital on May 24, 1937, at the request of her parents. She died at home on June 17, 1937, at the age of three. Death occurred fourteen months after the first treatment. Autopsy was not performed.

Summary and Conclusion

Carcinoma of the female external genitals in infants is very rare. A case of adenocarcinoma involving the vulva and the lowermost part of the

vagina is reported. Signs of the disease appeared when the child was five months old. A visible external lesion appeared when the patient was sixteen months old. Microscopic diagnosis was made when the child was twenty-one months old. This is one of the youngest cases, possibly the youngest case, of carcinoma in this site yet to be recorded in the literature.

References

1. Ritvo, M., Houghton, J. D., and McDonald, J.: Radiology **39**: 278, 1942.
2. Scotti, D. N.: New York State J. Med. **39**: 1188, 1939.
3. Kellert, E.: New York State J. Med. **39**: 2259, 1939.
4. Dargeon, H. W.: J. Pediat. **15**: 317, 1939.
5. Ewing, J.: Cancer in Childhood, Edited by H. W. Dargeon, St. Louis, 1940, The C. V. Mosby Co.
6. Morse, A. H.: Am. J. Obst. & Gynec. **19**: 520, 1930.
7. Kelly, J. A.: J. Pediat. **15**: 355, 1939.
8. Baldwin, L. G.: Am. J. Obst. & Gynec. **21**: 728, 1931.
9. Heckford, N.: Trans. Obst. Soc. Lond. **10**: 224, 1868.
10. Thomas, T. G.: Am. J. Obst. **7**: 45, 1874.
11. Lövegren, E.: Acta Paediat. **10**: 371, 1931.

HYPERNEPHROMA OF THE OVARY

Milton Kannerstein, A.B., M.D., Chester R. Brown, M.D., and James Alan Rosen, A.B., M.D., New York, N. Y.

(From Department of Pathology and Department of Obstetrics and Gynecology, Lincoln Hospital)

THE patient, a 52-year-old white woman, was admitted to Lincoln Hospital on Nov. 27, 1940, with the complaint of abdominal pain and cramps for twenty-four hours. She had been in her usual health, attending to her duties as a housewife until the day before when the above symptoms began. They were at first interpreted as an attack of biliary colic, similar to those from which the patient had suffered for many years. In twelve hours she had become weak and irrational. On admission she was in shock and stuporous. Pulse and blood pressure were not obtainable; heart sounds were poor. Temperature was 98° F. The abdomen was distended and tender. A large mass was present in the abdomen, nearly filling the left side which was dull to percussion. No evidence of free fluid was obtained. Pelvic examination revealed tenderness in the left pelvis but no intrapelvic mass. Urine revealed an occasional granular and hyaline cast. A bedside x-ray showed no free air in the abdomen.

The abdominal findings were interpreted as a possible acute diverticulitis with perforation. The patient was transfused but became weaker, comatose, and died eight hours after admission, approximately thirty hours after the onset of acute symptoms.

The past history revealed 2 normal full-term pregnancies and deliveries, the last 20 years ago. Since then the patient had suffered from occasional nocturnal attacks of typical biliary colic, but these passed within a few hours and she had never been jaundiced.

However, the significant part of the past history was that in 1929 she had developed severe hematuria and a diagnosis of renal tumor had

been made at another hospital. On Sept. 19, 1929, the right kidney was removed through a lumbar incision. It was found to contain a tumor "in its upper two-thirds, entirely within the substance of the kidney," measuring 8 by 10 by 5 cm. At no point had the tumor ruptured outside of the capsule of the kidney; it was entirely encapsulated. It had not extended into the ureter, renal artery, or vein (no mention is made of whether it extended into a calyx) and showed the typical appearance of a hypernephroma with a yellow appearance in places and a large gelatinous-like area of degeneration in the center and in other places a few small hemorrhages.

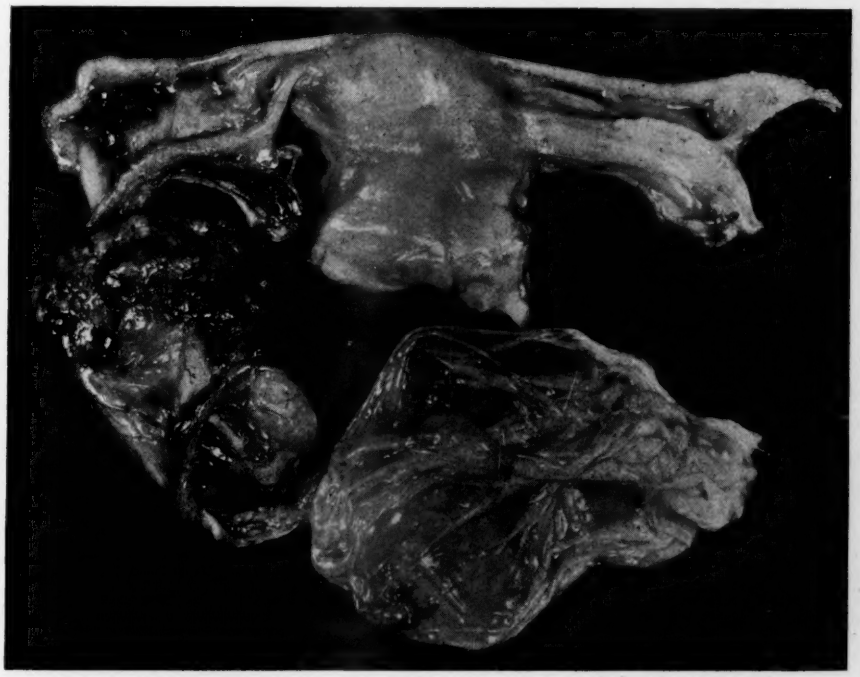

Fig. 1.—Uterus, posterior view, showing solid tumor attached to broad and round ligaments. A large thin-walled cyst is attached to the tumor.

Slides were no longer available but the microscopic report at the time read ". . . The tumor is a hypernephroma with areas of mucoid degeneration. It is definitely separated from the renal parenchyma by a fibrous capsule. Some small areas of hemorrhage and areas of edema. The pelvis is not involved and no large vessels are seen thrombosed by the tumor. Diagnosis: Hypernephroma of the kidney."

In 1931, the patient had a conization of the cervix for erosion and laceration. She had a natural menopause four years before the present illness and no vaginal bleeding since.

Autopsy

External Examination.—The body was that of a moderately obese middle-aged woman of normal habitus. No hirsutism was present. The external genitals were normal for the age. A left oblique lumbar scar was present.

Abdominal Cavity.—The abdominal cavity contained approximately 2,500 c.c. of blood, about 1,200 c.c. being clotted. In the left iliac fossa was a thin-walled cyst approximately 18 cm. in diameter. This was contiguous to and connected by a fibrous band with a smaller, ruptured cyst about 8 cm. in diameter, filled with clotted blood. The latter was attached to the broad and round ligaments of the uterus and lay about 10 cm. from the left cornu in the pelvis. On its posterior and medial (tubal) aspect was a bright yellow-orange solid irregular, somewhat loculated mass (ovarian tumor) approximately 3.5 by 3.5 by 4 cm. in size.

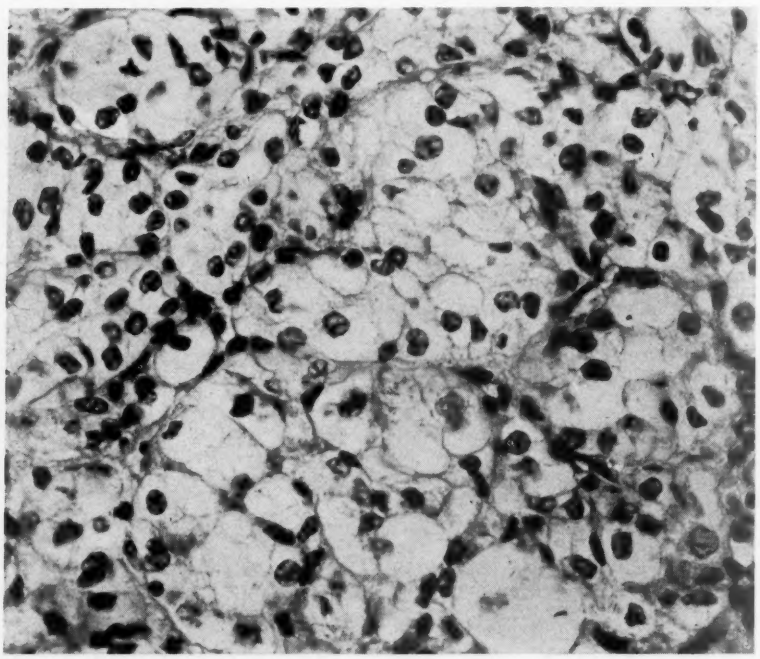

Fig. 2.—Section of ovarian tumor showing clear and granular cells with small round nuclei and thin reticulum.

This mass grew into and formed part of the cyst wall, spreading out for a short distance in plaque form on its inner surface. Section showed the tumor to have a moderately variegated appearance. Some areas consisted of homogeneous orange-yellow tissue containing a few small cysts. Other areas, especially those growing into the cyst, contained large, dilated blood-filled spaces, apparently channels, one of which, about 4 mm. in diameter, opened into the cyst and appeared to have been the site of bleeding. The rest of the cyst wall was smooth, thin, and translucent. There was no grossly identifiable ovarian tissue on the left side. The cysts and mass seemed to bear the relationship, though distorted, of the left ovary. The large cyst contained a clear, thin, light yellow fluid and was lined by a translucent membrane. The tubes, uterus, and right ovary were atrophic.

The right kidney was absent. The left was essentially normal.

Microscopic Examination.—The fleshier parts of the tumor showed closely packed alveoli, clearly shown by Bielschowsky stain to be surrounded by a thin reticulum, continuous from alveolus to alveolus. The

latter consisted of 8 to 12 large, polyhedral, or rounded cells with clear or granular eosinophilic cytoplasm, and small round or oval, for the most part dark, centrally located nuclei, without nucleoli. Occasional nuclei were moderately vesicular. Many were eccentric, even peripheral. An occasional cell appeared multinucleated, but no bizarre or giant forms were seen. No mitoses were noted. Occasionally there were transitions to tubules or acini lined by a single layer of cuboidal cells similar in other respects to the cells of the alveoli. The clear cell alveoli were present in clusters surrounded by groups of granular-cell alveoli. The latter cells were smaller. In the vascular parts were channels of all sizes consisting of an endothelial layer with little or no surrounding connective tissue. Some of the channels were enormous. In these areas columns and clumps of cells were outlined by vascular channels. Here and there the vascularity was so great and the channels so closely approximated as to leave no intervening tumor cells, but merely narrow bands of collagen. Cystic spaces of various sizes lined by flattened elongated cells and filled with homogeneous pink-stained material were seen in many sections. Necrosis was minimal. Occasional hemorrhagic areas were noted. Scarlet R stain showed the presence of large amounts of fat, filling many tumor cells completely and present, at least as granules, in most. Only a rare droplet stained pink with Nile blue sulfate, the rest staining blue green. No doubly refractile material was seen.

Discussion

We are inclined to regard the ovarian tumor in this case as a metastasis from the renal neoplasm. This opinion is based on the characteristic histology and the clinical history.

The histology is identical with the so-called Grawitz or hypernephroma type, which according to some authors arises from an adrenal rest in the kidney. Others (Stoerk, Schiller) believe this tumor is of renal tubular origin or arises from a "rest" of embryonal renal tissue within the kidney (Wilson and Willis, Geschickter). Most authors believe that the characteristic "clear-cell" variety is a more differentiated, less malignant type than the "granular-cell" kind. Although some prefer to call the former hypernephroma and the latter adenocarcinoma, it becomes more and more apparent that they are genetically identical and that the distinction is of value for clinical prognostic purposes only (Fouldes and Braasch, Hunt and Hager, Geschickter). Actually both granular and clear cells, alveolar and papillary formations, are present in most of these tumors, although one or the other may predominate (Bonnanor, Geschickter). In our case, cell structure was both clear and granular. Structure was chiefly alveolar, although a papillary appearance was present in one area. There was a distinct tendency to tubule formation which is characteristic of the renal hypernephroma (Geschickter, Schiller, and others). The presence of large, thin-walled blood sinuses is another suggestive feature. Primary hypernephroid ovarian tumors appear, from descriptions and illustrations, to be more uniform in structure, without tubule formation and not as vascular as the renal tumors or the one described here. According to Greenblatt and others primary ovarian hypernephroma contains crystalline doubly refractile and metachromatic (with Nile blue sulfate) droplets similar to those found otherwise only in adrenal adenomas and different from the pattern in renal hypernephroma. This we could not confirm. However, although this may

suggest that this tumor did not arise from an ovarian adrenal rest, it does not prove that it arose from a renal hypernephroma. Unfortunately, we were not able to obtain sections of the original renal tumor, but from the description there is no reason to doubt that it was a typical Grawitz tumor. Although eleven years may be considered a rather long interval for such a small metastatic tumor to manifest itself, especially in such an indirect manner, behavior of this type is almost characteristic of certain cases of hypernephroma.

Summary

1. Hypernephroid tumors, i.e., yellow tumors containing large lipid filled cells, of the ovary have been described over the course of many years. The tumors differ considerably in appearance and behavior. Some have been masculinizing; a few have produced precocious puberty. There has been and still is much discussion about the histogenesis of these tumors, some favoring an adrenal rest; some a lutein cell origin. There are many contradictions in each point of view, and great confusion about these tumors still exists. It is highly questionable if they do constitute a definitive group.

2. A case of such a tumor is presented, which is believed to have been secondary to a renal hypernephroma removed eleven years before. The ovarian tumor bled into a large serous cyst of the ovary and caused fatal intraperitoneal hemorrhage.

3. Renal hypernephromas and their metastases are bizarre in their behavior. Long time-intervals and peculiar manifestations from the metastases have been the subject of many papers. Ovarian metastases are very rare. This case constitutes the third, or possibly the fourth, on record.

Moore, John H.: The Late Effects of the Toxemia of Pregnancy, Journal-Lancet 61: 368, 1941.

The author reports his results after following 57 patients who could be classed as toxemias of pregnancy. He found only two diseases that appeared noteworthy in favoring the development of a toxemia of pregnancy and those were scarlet fever and recurrent tonsillitis. These diseases either alone or together were noted in 57 per cent of these cases. Fifty-nine per cent of the toxemias occurred in primiparous women. Ten premature and three full-term infants born to mothers with nephritic toxemia survived, a salvage rate of approximately 50 per cent; 20 infants (4 premature and 16 full term) born to mothers with pre-eclamptic toxemia survived including one set of twins, or a salvage rate of almost 87 per cent. Eight of the nine babies born to eclamptic mothers, or 88 per cent, survived. The incidence of twins in these groups was 5 per cent.

In 19 patients with a nephritic type of toxemia, there was a survival of 12 infants in 29 subsequent pregnancies. In 13 patients of the original group of 23 who were diagnosed as pre-eclamptic toxemia seven showed evidence of nephritis in subsequent pregnancies, four had questionable cardiorenal vascular disease, and only two had no untoward symptoms or incidents to mar their subsequent pregnancies. The pre-eclamptic and the eclamptic group, while they showed no mortality, gave evidence of recurrent toxemia or of permanent cardiovascular renal changes in 83 per cent of the cases in subsequent pregnancies.

WILLIAM BERMAN.

BILATERAL MICROCYSTIC DEGENERATION OF THE OVARIES AND MASCULINIZING SYNDROME

SAMUEL J. TURNER,* B.S., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Illinois College of Medicine and the Mount Sinai Hospital)

EXTENSIVE masculinization in association with microcystic disease of the ovaries is a very uncommon condition. Two cases of this syndrome recently reported by Geist and Gaines[2] displayed a bilateral follicular degeneration of the ovaries with striking proliferation and luteinization of the theca interna. Numerous clusters of luteinized cells were also found throughout the ovarian stroma. The cases described had both ovaries removed. One of the patients who was followed showed no evidence of clinical improvement after operation.

Stein, Leventhal and Robinson[3-5] obtained gratifying results by resecting polycystic ovaries in patients with amenorrhea and sterility. Normal menstruation was re-established in almost all of their cases. Some of the patients became pregnant and gave birth to normal living children. The ovarian tissue was described as having a thick tunica with numerous cysts of varying size lined mostly by an hypertrophied thecal layer with scarce granulosa cells.

The following case showed pathologic and clinical changes which were quite similar to those found by Geist and Gaines.[2] A different end result was obtained, however, by resecting instead of removing both ovaries.

Case Report

A. S. (History No. 103829), single, 23-year-old factory worker, presented herself on Aug. 20, 1940, complaining of amenorrhea and growth of hair on the face and abdomen of six months' duration. The hirsutism became very pronounced and she tired easily during the past two months. No significant facts were elicited from her family or past history except that her mother was a diabetic. Her menses began at 14 years, four to seven weeks' interval, four to five days' duration, moderate flow without associated symptoms. The last menstrual period occurred in February, 1940.

Examination revealed a moderately obese 23-year-old white female, appearing very nervous but not acutely ill. Temperature was 98.6° F.; pulse, 96; blood pressure 132/80. The chin had a luxurious growth of thick blond hair in spite of the fact that she had shaved within a few days. The breasts were smaller than expected in an obese female of her size. The heart, lungs, and abdomen were normal. Pelvic examination, which was done under anesthesia, revealed a masculine type escutcheon, an atrophic labia majora and minora, an hypertrophied clitoris to 2.5 cm. in length, a narrow vagina admitting two fingers with difficulty, and a very narrow short cervix with a pin-point orifice. The corpus uteri was double the size of the cervix but also very small. Both ovaries were readily palpable. The right ovary seemed to be larger than the corpus uteri. The left ovary was smaller. The Fallopian tubes were not palpable.

*In Service as First Lieutenant, M. C., A. U. S.

X-ray examination of the sella turcica was negative. X-ray visualization after injection of air into the suprarenal spaces revealed no evidence of adrenal enlargement. There was a slight trace of albumin in the urine. The blood Kahn was negative. A complete blood count and blood chemistry was found to be within normal limits. The basal metabolic rate was plus 8.

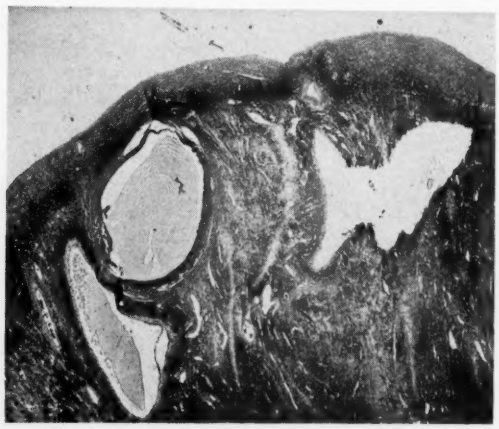

Fig. 1.—Low-power section of the ovary showing cystic follicular degeneration with marked density of the ovarian stroma.

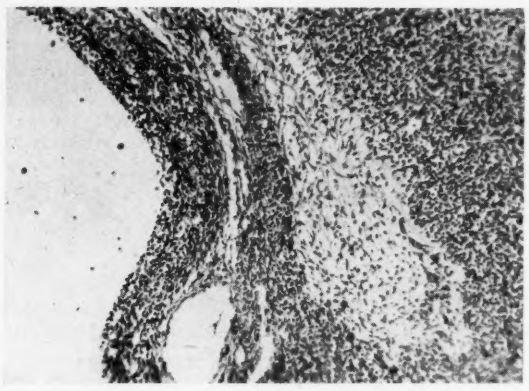

Fig. 2.—High-power section presenting a narrow well-defined granulosa layer, a wider well-developed luteinized theca interna, and a cluster of lutein-like cells within the ovarian stroma at some distance from the follicle.

The preoperative diagnosis was masculinizing tumor of the right ovary. A dilatation and curettage and a laparotomy through a midline incision was done. A very small amount of endometrium was obtained. The uterine cavity was only 1 cm. in length. Both ovaries were studded with small follicular cysts. The right ovary was almost twice the size of the corpus uteri and the left ovary was almost as large as the corpus uteri, which measured about 4 by 2 by 2 cm. The Fallopian tubes were normal. An incision into both ovaries disclosed widely scattered follicular cysts throughout the cortical tissue. The cysts contained a clear mucinous fluid. Two-thirds of each ovary was resected and the remaining cysts were carefully punctured and emptied. Both adrenals were

palpated through the abdominal cavity and were found to be of normal size. The appendix was removed and the abdomen closed.

Microscopic study of several regions of the available ovarian tissue disclosed no evidence of an androgenic tumor. The follicles were cystic and widely scattered throughout the cortex. Most of the follicular walls contained a well-defined narrow granulosa layer with a much wider well-developed theca interna showing distinct luteinizing characteristics. The stroma was dense and contained clusters of luteinlike cells at some distance from the follicles. The endometrial glands were small, poorly defined, with a tendency toward secretory activity; the intervening stroma contained a large number of red blood cells.

Fig. 3.

Fig. 4.

Fig. 3.—Endometrium obtained during the operation showing marked atrophy with poorly defined small glands and a tendency toward secretory activity.

Fig. 4.—Endometrium obtained about sixteen months after operation during the twentieth day of the cycle showing an abundant amount of endometrium in a well-developed proliferative phase with some evidence of secretory activity.

The patient left the hospital on the tenth day after operation. A normal menstrual flow of seven days' duration occurred in four weeks and has been recurring periodically every twenty-eight to thirty days. No additional evidence of hirsutism appeared after the existing hair was removed by electrolysis. The breasts have become larger and normal in appearance. The hair on the abdomen has almost completely disappeared, and the escutcheon hair has become characteristically female. An endometrial biopsy was done twenty days in the cycle about sixteen months after operation and an adequate amount of endometrium was obtained. Microscopic study revealed a well-developed proliferative phase with some evidence of secretory activity. The uterine cavity measured 6 cm. in length and the uterus seemed to be normal in size.

Comment

Our present-day knowledge of endocrinology does not explain the exact mechanism which causes the masculinization syndrome in the presence of luteinized microcystic degeneration of the ovaries.

Geist and Gaines[2] are of the opinion that the ovarian changes are incidental findings with the masculinizing syndrome. The case which they observed after operation did not improve even after both ovaries were removed. They also quote Bergstrand who had a case similar to theirs which revealed a basophilic adenoma of the pituitary and a diffuse hyperplasia of both adrenal glands at autopsy. They, therefore, concluded that the syndrome was primarily caused by pituitary basophilism or adrenal cortical lesions. The end result in my patient does not bear out their contention. Since no recurrence of symptoms was noted when she was last seen about two years after operation, it is safe to infer that the pathologic changes in the ovaries were the primary factor for the syndrome.

No facilities for blood and urine hormone determinations were available at the time. The evidence of secretory activity of the atrophic endometrium and the marked luteinizing changes of the ovaries would tend to support the possibility that a large amount of progesterone was present in the body. Perhaps the masculinizing changes which occurred here may have been associated with or due to an excess amount of progesterone as one frequently sees in cases of adrenal cortex neoplasms.[1, 6, 7] Resection of the ovaries apparently re-established a normal endocrine balance with a very good clinical result.

Summary and Conclusions

1. The case presented had a far-advanced masculinizing syndrome which was associated with microcystic degeneration of the ovaries, a marked luteinization of the theca interna, and some luteinization of the ovarian stroma.

2. Resection of two-thirds of each ovary and puncture of the available cysts resulted in restoration of regular periodic menstruation, growth of the uterus to the usual normal size, decrease in the size of the clitoris, enlargement of the breasts, and cessation of the growth of hair on the face and abdomen.

References

1. Butler, G. C., and Marrian, G. F.: Biol. Chem. **119**: 565, 1937.
2. Geist, S. H., and Gaines, J. A.: AM. J. OBST. & GYNEC. **43**: 975, 1942.
3. Leventhal, M. L.: AM. J. OBST. & GYNEC. **41**: 516, 1941.
4. Robinson, M. R.: AM. J. OBST. & GYNEC. **30**: 18, 1935.
5. Stein, I. F., and Leventhal, M. L.: AM. J. OBST. & GYNEC. **29**: 191, 1935.
6. Salmon, V. J., and Geist, S. H.: Proc. Soc. Exper. Biol. & Med. **47**: 279, 1941.
7. Venning, E. H., and Weil, P. G.: J. Biol. Chem. Sc., Proc., p. 128, 1939.

HYDATIDIFORM MOLE IN A TWIN PREGNANCY, WITH A PREMATURE LIVING INFANT

EDWARD G. WATERS, M.D., F.A.C.S., AND ALLEN B. CRUNDEN, M.D.,*
JERSEY CITY, N. J.
(From the Margaret Hague Maternity Hospital.)

THE finding of hydatid changes of varying degrees in early pregnancy in association with pathologic or so-called blighted ova is common. Meyer[8] in his work on specimens in the Mall collection found that about one-third of uterine abortions showed definite molar degeneration. He calculated that at least 10 per cent of all conceptions end in hydatid degeneration, thus making it one of the most common diseases of the placenta and fetus during the early months of gestation. However as pregnancy approaches term such changes are progressively more uncommon, or even rare.

Cases of typical hydatidiform moles coexisting with a well-developed fetus occasionally have been reported. As Bland[2] points out, the existence of a well-developed fetus and an advanced mole in the uterus at the same time would seem physically impossible except in a plural pregnancy. The suggestion of a twin pregnancy is even more striking in those cases in which the primary expulsion of a fetus with membranes and placental tissue is followed several hours later by the expulsion of a mole. However, the simultaneous expulsion of mole and fetus has likewise been observed.

There are numerous reports of such cases in the literature. Brews[4] had two cases of twin pregnancy each with a normal fetus of about fourteen weeks coexisting with a hydatidiform mole. Kangas,[6] Meyer,[8] Speiser,[9] Strauch,[10] among others, have published similar records.

Clinical reports of live normal infants associated with a hydatidiform mole, as seen in the present case, are few. In recent years Beasley,[1] and Favreau and Belanger,[5] have reported cases of a normal infant at term with a typical mole.

Report of Case.—Mrs. M. S., a white woman, 24 years of age, history No. 37250, was a nonclinic gravida ii, whose last menstrual period was July 20, 1938, and the expected date of confinement April 27, 1939. Her prenatal course had been apparently uneventful. She was admitted on March 28, 1939, in labor with a history of a moderate bloody show for the previous two hours. Her bag of waters had ruptured just prior to the onset of pains.

Her previous pregnancy had been entirely normal with a natural delivery of a normal full-term infant at home. The patient's health had always been good except for childhood diseases.

Physical examination revealed a well-developed and well-nourished woman in early labor. Blood pressure was 130 systolic, 80 diastolic, pulse rate was 112 per minute, and temperature 99.2° F. The uterus was symmetrically enlarged, reaching to just above the umbilicus and was slightly tender. Fetal parts could be palpated and the fetal heart was audible in the right lower quadrant, rate 156, and of good quality; cephalic presentation. Because of a rather profuse bloody

*At present in Service, Army Air Forces, School of Applied Tactics.

show, rectal examination was deferred. Diagnosis was pregnancy at thirty-six weeks, with possible placenta previa.

Patient was taken immediately to the delivery room, where labor progressed very rapidly. On vaginal examination the cervix was found to be fully dilated, and the vagina contained considerable free blood. A rather small infant was delivered spontaneously, occiput right anterior, following a few uterine contractions.

Search for the source of the bleeding was made immediately. A disc-shaped mass resembling a placenta without cord was found in the vagina, and it delivered spontaneously. On the posterior lip of the internal os was a firm mass, apparently a small intramural fibromyoma, which pushed the internal os upward, the whole projecting through the internal os. This was pushed up manually and the cervix plicated at the sides with chromic catgut to maintain it.

The placenta was expelled intact after a third stage of ten minutes and following this 1 c.c. of ergometrine was administered intramuscularly. Total blood loss was estimated at 400 c.c. from the time of admission.

The infant breathed spontaneously, had a vigorous cry, and weighed 2,150 Gm. A thorough examination revealed no abnormalities. She was placed in the premature nursery, had an uneventful neonatal course, and was discharged on the forty-first day weighing 3,000 Gm.

The mother had a normal post-partum period. Following an initially positive Aschheim-Zondek test twenty-four hours post partum, all further tests have been negative. When last contacted two years following delivery, she had had no further pregnancies and her Aschheim-Zondek test was negative.

The pathologist, Dr. Nicholas M. Alter, reported as follows:

Specimens consisted of two placentas. The first weighed 435 Gm. and was 17 by 15 by 3 cm. The cord was eccentrically inserted and rather long. The fetal surface was smooth and the maternal surface showed only a few irregular opaque white spots varying from 1 to 3 m.m. in diameter. Microscopic sections showed thin villi with well-developed and slightly congested blood vessels. They were covered by thin atrophic chorionic epithelium. The diagnosis was normal placenta. The second placenta-like mass weighed 475 Gm. and had approximately the same measurements. There was no evidence of a cord. Fetal membranes were present, but there was no evidence of a fetus. The fetal surface was quite pale and obviously thickened. The decidual surface was irregular, nodular, and uneven. Within torn areas cystic structures were seen having varying diameters. Numerous cross sections through the mass revealed very little solid tissue. Microscopic sections showed cystic villi with fibrosis. No normal villi or blood vessels were seen. The tissue was made up of cystic structures some of which were filled with dark-celled myxomatous tissue and covered by moderately hyperplastic chorionic epithelium. Diagnosis was hydatidiform mole.

Discussion

An unusual case of a hydatidiform mole occurring in a twin pregnancy with a premature living infant is reported. The importance of the phenomenon other than its obscurity is the opportunity given to emphasize again the need for follow-up in all such cases of twin pregnancy as possible sources of a later chorionepithelioma. Matthieu and Palmer[7] reported a case with a three months' fetus in which there

developed a chorionepithelioma two months afterward. In a similar case, Bland[2] depicted the transition of a benign hydatidiform mole to a perforating or malignant mole and finally to a highly malignant chorionepithelioma. The clinical diagnosis of an abortion may seem correct and obvious with a fetus alone, and the true diagnosis of hydatidiform mole thus be obscured. Brews[3] reported three cases of chorionepithelioma following abortions which "may have been hydatidiform moles" by clinical history, but not confirmed by pathologic study.

The fact that such a case as the one here reported can occur would seem to strengthen the hypothesis that hydatid mole originates as the result of some intrinsic abnormality of the ovum, rather than one present in the harboring maternal structures.

References

1. Beasley, B. T.: South. M. J. **25**: 585, 1932.
2. Bland, P. B.: Am. J. Obst. & Gynec. **13**: 189, 1927.
3. Brews, A.: Proc. Royal Soc. Med. **28**: 69, 1935.
4. Brews, A.: J. Obst. & Gynec. Brit. Emp. **46**: 813, 1939.
5. Favreau and Belanger: Bull. Soc. gynec. et d' obst. **28**: 179, 1939.
6. Kangas, T.: Duodecim **52**: 130, 1936.
7. Matthieu, A., and Palmer, A.: Surg., Gynec. & Obst. **61**: 336, 1935.
8. Meyer, A. W.: Contributions to Embryology **12**: 1, 1921.
9. Speiser, M.: Zentralbl. f. Gynäk. **56**: 1465, 1932.
10. Strauch, H.: Zentralbl. f. Gynäk. **62**: 1371, 1938.

39 Gifford Avenue.

DOUBLE MONSTER, PYGOPAGUS

John L. Keyes, M.D., Lexington, Ky.

(From the Obstetrical Service of the Good Samaritan Hospital)

THIS 24-year-old white woman was admitted to the Good Samaritan Hospital on Oct. 11, 1942. Her last menstrual period had been on Jan. 28, 1942, making her delivery due November 4. Her past medical history was essentially negative. She had had one previous pregnancy in 1940, which had gone to term, and she had a spontaneous delivery of a viable child weighing 8 pounds 7 ounces after a six-hour labor. She had a post-partum hemorrhage and was given three transfusions.

This pregnancy had been uneventful up to the time of admission. Wassermann and Kahn tests were negative. Urinalysis had been negative and blood pressure on admission was 98 systolic and 64 diastolic. Contractions had started a short time before coming to the hospital and the membranes had ruptured. The abdomen was large and two fetal hearts could be heard. About an hour after admission two feet presented at the vulva and she was taken to the delivery room. An unsuccessful attempt at breech extraction was made. Trying to determine the cause of the dystocia a hand was inserted into the uterus and another foot could be felt which seemed to be smaller than the two presenting. It was assumed that the second twin was in some way interfering with the delivery of the first but the true condition was not recognized. Two fetal hearts could still be heard, so it was decided to perform a cesarean section. A classical section was done and the monster delivered through a long incision in the uterus. The patient bled considerably, due to the overdistention of the uterus, but was in pretty good condition on return to her room. A transfusion was given on the third day. She showed no

signs of infection and had a smooth convalescence, leaving the hospital on the eleventh day.

At the time of delivery the baby on the right, designated as "A," started crying and had a good color. The baby on the left, designated as "B," was cyanotic and appeared lifeless. About two hours after birth, B started breathing and its color improved, but was never as good as that of A. Both babies were hydrocephalic. There was one cord which went to A. B had the remnants of an umbilicus and a stringlike cord about three inches long. The monster weighed eleven pounds and

B. *A.*

Fig. 1.

twelve ounces. B had a cleft palate. The babies were fused at the sacrums. There were one anus and one external genital which were edematous and dark in color. The two legs and feet forward were of the same size and were loosely connected to the body. From the position of the great toes apparently one of these two extremities belonged to each baby despite the difference in size between them and the other two extremities which were of the same size and were the two presenting. They voided and passed meconium normally.

The placenta was large and had only the one cord which went to A.

The monster lived for forty-eight hours. Autopsy showed the organs above the diaphragm normal in appearance. Livers and spleen appeared

normal. Each fetus had a right kidney but none on the left side. A had one adrenal gland and B had two. The intestinal tracts opened into a common cloaca just above the common anus. Each had a uterus, tubes, and ovaries. Each had a vagina that opened between the common

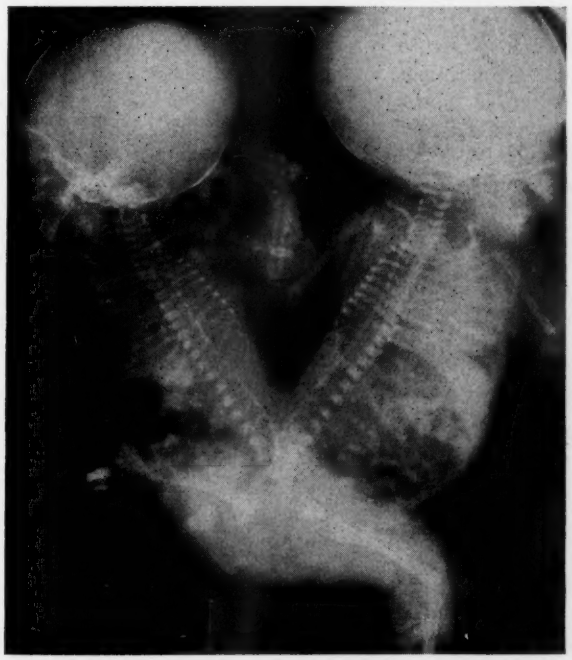

Fig. 2.

labia. None of the organs were opened because the parents had agreed to give the specimen to the University for further study. Later they changed their minds and carried out a burial.

References

1. Mortimer, B., and Kirshbaum, J. D.: Am. J. Dis. Child. 64: 697, 1942.
2. DeLee, J. B.: Principles and Practice of Obstetrics, ed. 5, Philadelphia, W. B. Saunders Co., p. 582.
3. Puech, cited by Scammon, R. E.: Fetal Malformations, in Abt, I. A.: Pediatrics, Philadelphia, 1925, W. B. Saunders Company 6: Chap. 164, p. 654.
4. Hirst, J. C.: Monsters, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, 1939, F. A. Davis Company, Vol. 10.

200 West Second Street

VITAMIN B FACTORS IN TOXIC PSYCHOSIS OF PREGNANCY AND THE PUERPERIUM

B. F. Hart, M.D., Winter Park, Fla., and W. T. McConnell, M.D., Louisville, Ky.

FROM experience with two cases it appears that psychosis in pregnancy and the puerperium may in some cases be associated with disturbances in vitamin B metabolism.

Last year, at the Louisville General Hospital, a patient was admitted with pernicious nausea and vomiting of pregnancy. She received the usual therapy, consisting of intravenous fluids and small dry feedings for a period of two weeks. At the end of that time she had developed neuritis, reddened tongue, and a psychosis. Moderately large doses of vitamin B components: 100 mg. of thiamin chloride, 100 mg. of niacin, 50 mg. of pyridoxine hydrochloride, 50 mg. of pantothenic acid, and 10 mg. of riboflavin were given intravenously each day for three days. At the end of that time the nausea was gone, the neuritis improved, and the psychosis was better. Intense therapy was continued orally and by the end of a week all symptoms disappeared. She went to term and delivered normally. Since psychosis is often associated with niacin deficiency, it was assumed that hers was likely on this basis.

More recently a private patient, who had developed eclampsia and was treated conservatively by her family physician until the convulsion ceased, was referred to Dr. McConnell who delivered her by cesarean section. The postoperative course went smoothly until about thirty-six hours at which time the nurses met her in the hall. She said, "My room is full of soldier boys and blue lights are flashing from the fixtures." She was put to bed and kept there only by the constant attendance of a nurse.

On the basis of the previous experience we decided to give nicotinamide and thiamin chloride in large doses. She received 300 mg. of each intravenously in divided doses during the first twelve hours and a total of 900 mg. of each over seventy-two hours. Within twenty-four hours her mental condition had cleared. The medication was discontinued after three days. There was no recurrence of her symptoms.

Neither of these patients had any insanity or other nervous diseases in the family background. Both of them had had clear-cut toxic disturbances before the onset of the psychosis. This mode of therapy seems worthy of further trial.

It would also be interesting to try this treatment on those patients who develop psychosis comment after severe infections.

Two patients who developed psychosis after toxic disturbances in pregnancy responded to therapy with vitamin B components. The niacin was probably the most important factor.

References

Freudenberg, R.: Wien. klin. Wchnschr. **50**: 535, 1937. (Abst. J. A. M. A. **109**: 93, 1937.)

Aring, C. D., Evans, J. P., and Spies, T. D.: J. A. M. A. **113**: 2105, 1939.

Cleckly, H. M., Sydenstricker, V. P., and Geeslin, L. E.: J. A. M. A. **112**: 2107, 1939.

Frostig, J. P., and Spies, T. D.: Am. J. M. Sc. **199**: 268, 1940.

Sydenstricker, V. P.: Ann. Int. Med. **14**: 1499, 1941.

Sydenstricker, V. P., and Cleckley, H. M.: Am. J. Psychiat. **98**: 83, 1941.

Hart, B. F.: Florida State M. J. **29**: 128, 1942.

INVERSION AND PROLAPSE OF A RUPTURED UTERUS DURING LABOR, TREATED BY IMMEDIATE VAGINAL HYSTERECTOMY*

PAUL C. FOX, B.S., M.D., F.A.C.S., OAK PARK, ILL.

THIS case is reported because of the unusual sequence of events and the successful treatment.

Mrs. X., aged 42 years, gravida vi, para v, entered the West Suburban Hospital at 2:30 P.M., August 31, 1942. She was at term but not in labor. Examination was essentially negative except that the patient was very obese, weighing about 190 pounds. Diagnosis of transverse presentation was made by the attending physician.

Past obstetrical history was as follows: First pregnancy, normal delivery, 10-pound boy, November, 1923; second pregnancy, normal delivery, 6-pound girl, December, 1925; third pregnancy, forceps delivery, 10½-pound boy, stillborn March, 1936 (patient was in labor two days before this delivery); fourth pregnancy, forceps delivery of a stillborn 10-pound girl (patient had premature rupture of the membranes about two weeks before and had high fever following this delivery); fifth pregnancy, normal delivery, 7-pound girl, May, 1939. She was five days past the date of expected confinement with her sixth pregnancy. Last regular period, Nov. 18, 1941: Expected date of confinement, Aug. 26, 1942. Her prenatal course was uneventful but since she did not go into labor at the expected time, and because of the history of large stillborn babies, the attending physician sent her into the hospital for induction of labor.

At 9:00 P.M., August 31, labor was induced with castor oil and quinine. Mild pains started promptly and the membranes ruptured spontaneously at 11:30 P.M. Mild labor continued through the night.

At 9:30 A.M. September 1, a large amount of meconium was passed. Vaginal examination at 10:00 A.M. disclosed a frank breech presentation. The cervix was 4 cm. dilated and the breech was at station minus one. Fetal heart tones were slightly irregular. The patient was having mild labor pains.

At 10:15 A.M. the attending physician ordered pituitrin minims 2. This was repeated at 10:30 and again at 11:15, making a total of 6 minims of pituitrin in one hour.

At 11:30, fifteen minutes after the last dose, the patient complained of excruciating pain in the left lower abdomen and began to have frank vaginal bleeding. There was no evidence of shock. This pain lasted about ten minutes and then gradually subsided. At this time the fetal heart tones became irregular and were not heard after 11:45 A.M.

At 12:00 noon another vaginal examination was made by the attending physician and at this time he could not feel the presenting part. The first consultant was then called in. Examination by this consultant showed that the cervix was fully dilated and that a boggy mass, which he thought to be an ablatio placenta, filled the cervix. He then noted that his hand was apparently inside the abdominal cavity and

*Presented at a meeting of the Chicago Gynecological Society, November 20, 1942.

that the fetus was in the uterus to the right of his hand and in an oblique position. He was able to bring down the anterior leg and then to extract a stillborn, 8½ pound boy.

Unsuccessful attempts were then made to express the placenta and a manual removal was attempted. During this procedure the uterus suddenly became inverted and delivered outside the vulva. Evidently the torn edge of the uterus was mistaken for the placenta and traction on it inverted the corpus through the rupture in the lower uterine segment. The placenta was not attached to the uterus but remained inside the abdomen. The consultant immediately corrected the inversion by turning the corpus right side out through the torn area. He was unable to replace the uterus in the pelvic cavity.

The second consultant was then called and found a complete extraperitoneal prolapse of the fundus with both tubes, both round ligaments and the left ovary visible. There was a large tear in the left lower uterine segment extending from the left round ligament down to the cervix. The cord was protruding through the vagina below the uterus. The patient's condition was fair but she was continually losing blood.

The only method of treatment that seemed at all reasonable or possible under these circumstances was to do an immediate vaginal hysterectomy. This was easily accomplished by starting from the fundus and working down toward the cervix. Both broad ligaments, including the tubes and round ligaments, were clamped and ligated. When the area of the lower uterine segment was reached, the bulk of the fundus was amputated. This gave access to the anterior vaginal wall which was now reflected, followed by the reflection of the bladder. The parametria were then clamped and ligated and the remainder of the uterus removed. A tight pack was inserted into the opening in the vaginal vault and the entire vagina was tightly packed. Before doing the hysterectomy, the placenta was found to be free in the pelvic cavity and was easily removed.

The patient had all of the usual restorative measures, including plasma, glucose solution and whole blood intravenously, which were started soon after the patient showed signs of ruptured uterus. She also received large doses of sulfathiazole. Her convalescence was remarkably smooth. During the first two days she had marked abdominal distention, which responded promptly to prostigmin and enemas. Her temperature at no time went above 101° F. The vaginal pack was removed in 24 hours and there was no further bleeding. The patient left the hospital on the 14th postoperative day.

This case again illustrates the danger of using even small doses of pituitrin during labor especially in a questionable presentation. It also presents an unusual cause for inversion of the uterus. Apparently the tear in the uterine wall was mistaken for the placenta and as it was being pulled down for inspection the uterus suddenly inverted.

Vaginal hysterectomy was the only feasible method of dealing with these complications. The fact that in this case, the presence of a large tear in the uterus made it possible to correct the inversion and perform a vaginal hysterectomy, suggests the possibility of treating inversion by making an incision in the uterus to correct the inversion and following this by vaginal hysterectomy. This procedure may be worthy of trial in certain selected cases.

715 LAKE STREET

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

AN EVALUATION OF THE METHODS FOR TREATING NON-MALIGNANT UTERINE BLEEDING IN THE MENOPAUSE

J. ROBERT WILLSON, M.S., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital)

THE choice between hysterectomy and irradiation castration for the control of benign menopausal bleeding from the normal-sized uterus, the fibrous uterus, or that associated with myomas must be governed by several factors. Questions which must be answered before a decision as to type of treatment is made are: (1) are the two methods comparable in effectiveness? (2) is the associated morbidity and mortality appreciably higher for either of the procedures? (3) is the incidence of uterine carcinoma following irradiation high enough to be a distinct hazard? and (4) is either method of treatment contraindicated for any individual patent? In the following discussion an attempt will be made to evaluate the methods of treating this selected group of patients.

Indications and Contraindications

In general the contraindications for either of the two methods of treatment may be used as an indication for the other. The patients in whom the removal of the uterus is contraindicated are those who are poor risks for any major surgical procedure. Included in this group are the obese individuals in whom operation would be hazardous and difficult, those with degenerative diseases such as diabetes and cardiovascular renal disease, those with blood dyscrasias, and the aged individual whose life expectancy is short.

The upper limits of uterine size usually considered acceptable for radium treatment is that comparable to a ten to twelve weeks' gestation. Deep x-ray therapy may be used effectively in this size tumor as well as in those which are much larger; in the latter, however, operative removal is usually a preferable procedure. The primary effect of both x-ray and radium is the inhibition of ovarian function. The latter, however, also produces sclerosis of the endometrium which aids in stopping the bleeding. Thus the insertion of radium in the larger myomas may fail to control bleeding completely because the large cavity and the thick uterine wall increase the distance from the source of radiation to a point at which the ovaries are not effectively irradiated.

Enlarged uteri producing symptoms other than bleeding should be removed if possible since treatment by castration, while it may stop bleeding, does nothing to relieve the associated symptomatology. Most enlarged uteri become smaller after cessation of ovarian function, but the amount of regression and the extent to which the symptoms will be relieved cannot be predicted. Degenerated fibroids obviously are best

treated by surgical removal. Since the bleeding from pedunculated submucous myomas often is from actual destruction of the tumor rather than from the endometrium the insertion of radium may, in some cases, increase the necrosis in the neoplasms and exaggerate rather than relieve the symptoms. If the endometrium over a submucous myoma is very thin, the destruction from the radium may be followed by local infection and occasionally sepsis. Pedunculated subserous fibroids may degenerate following irradiation as a result of a decrease in available blood supply and are best treated surgically.

Patients who have had either previous pelvic surgery or pelvic inflammatory disease often are not good candidates for irradiation. Loops of bowel which may have become adherent in the pelvis are likely to receive destructive doses of radiation resulting in stricture, and quiescent inflammatory processes may be activated. The palpation of adnexal masses contraindicates radiation therapy because of the impossibility of diagnosing accurately the type and extent of the pathology present by bimanual examination alone.

The common association of x-ray or radium with the treatment of malignant tumors may, as a purely psychologic measure, be an indication for hysterectomy. Irradiation, if forced upon the patient, may be followed by undesirable mental reactions even though the result of therapy be perfect.

Age of the patient must be one of the primary considerations before a plan of therapy is outlined. Since both radium and x-ray therapy destroy ovarian function, neither is the treatment of choice for the younger individual in whom the uterus can be removed and the ovaries, if normal, retained. Taussig sets the lower age limit for irradiation at 42, but in certain patients in whom menopausal symptoms are already present irradiation may be justifiable earlier.

Technique of Irradiation

The desired effect, castration with control of the bleeding, may be accomplished satisfactorily by adequate dosages of either radium or deep x-ray therapy. Brown and others have demonstrated that the lower the total dosage of radium the less likely is permanent castration to follow and therefore recommend the administration of about 2,000 mg. hours of intrauterine radium or radon irradiation to effect control of the bleeding. Although ovarian function can be inhibited in some instances by much smaller dosages, it is well to use an adequate amount of irradiation for each patient since the tolerance of individual ovaries cannot be measured. Because the desired effect from the use of radium is primarily inhibition of ovarian function rather than a local action on the endometrium the penetrating gamma rays must be utilized fully. The local destruction produced by the soft beta rays may be prevented by the use of a capsule with a filtration capacity equivalent to that of 2 mm. of brass. A thin layer of rubber or some other organic material around the capsule will filter out the secondary soft radiation from the capsule; the resultant radiation should be almost entirely from the gamma rays and the local tissue destruction will be reduced to a minimum.

Because of the necessity for delivering the radiation to the endometrium and the ovaries the radium should be applied to the cavity of the uterus and not in the cervical canal. This method results in a maximum radiation of the desired structures without danger of destruction of the cervix. Obviously the duration of the application depends upon the

amount of radium used, but in most instances no more than 100 mg. of radium or radon should be inserted for castration.

Brown and his co-authors also describe the technique for the administration of external irradiation and present dosage tables calculated to deliver 625 roentgen, a castration dose, to the ovaries in various sized individuals.

Either procedure must be proceeded by evaluation of the patient, thorough pelvic examination and curettage to rule out malignancy. If at the time of pelvic examination under anesthesia a condition which contraindicates radiation is discovered the plan of treatment should be altered.

Effectiveness

Obviously removal of the uterus will stop the bleeding in all instances. This may also be accomplished by the administration of sufficient amounts of radiation properly to selected patients; failures can for the most part be explained. The cessation of bleeding following reradiation in patients to whom inadequate initial dosages were given must be classified as successful. The failure of the bleeding to respond in improperly chosen cases or with too little treatment cannot be classified as a failure of the method. Many patients may have one or two periods of bleeding following irradiation; consequently evaluation of results cannot be made immediately. With the exception of a small number of unexplained failures a continuation of bleeding after irradiation usually is an indication of the improper selection of cases or of an amount of therapy too small to affect ovarian function.

Morbidity and Mortality

The mortality and morbidity following the irradiation of a well-selected group of cases should be much lower than that following surgery in a comparable group. The average morbidity in collected cases is only 0.3 per cent for the irradiated group. In most instances the morbidity following irradiation is represented by an unexplained temperature elevation which may be due to a mild exacerbation of a chronic pelvic inflammatory process or to local tissue destruction. Occasionally, following the insertion of radium, a quiescent inflammatory lesion may develop into a serious acute infection with abscess formation and peritonitis.

The inevitable mortality from hysterectomy should be reduced to a minimum in operations for benign menopausal bleeding. The mortality rate of 2.5 per cent for 16,165 collected subtotal hysterectomies reported by Cashman and Frank, however, does not approach that of 0.05 per cent following irradiation in 8,175 cases. Many authors are of the opinion that the mortality rate is even higher when complete hysterectomy is performed. This obviously is a point in favor of irradiation. Danforth, on the other hand, has reported a series of hysterectomies with a total mortality rate of only 0.5 per cent. In this group the mortality rate for total hysterectomy was 0.66 per cent, for subtotal 0.8 per cent, and for vaginal hysterectomy 0 per cent.

Carcinoma Following Treatment

The incidence of uterine carcinoma developing following irradiation is 0.5 per cent in 6,883 cases collected from the literature. Since it is sometimes impossible to detect early corpus carcinoma even by careful curettage and since a few of these cases developed within a relatively short period of time after therapy, it is not unreasonable to assume that some of the malignancies were present when the treatment was instituted

and thus cannot be considered as a result either of irradiation or of leaving the uterus.

Removal of the uterus and the cervix in every patient would, of course, completely eliminate the development of uterine carcinoma, but subtotal hysterectomy does not since the incidence of carcinoma developing in the cervical stump is about 0.6 per cent or the same as that following irradiation. This incidence of stump carcinoma, however, may also be high since many of the cases reported were diagnosed within a few months of the time of hysterectomy and may have been overlooked during the original operation. Martzloff suggests that any cervical malignancy developing within three years of the hysterectomy may have been present and undiagnosed. Even though the mortality rate for total hysterectomy was the same as for subtotal it is doubtful that it would be less than the combined mortality from irradiation and carcinoma developing in the irradiated uterus.

The Present Status of the Treatment of Benign Menopausal Bleeding

In an effort to obtain information concerning the present status of the treatment of benign menopausal bleeding, a questionnaire was sent to a representative group of gynecologists throughout the United States. A tabulation of the data (Table I) reveals that 79 per cent of those contacted favor irradiation castration for the treatment of menopausal bleeding from the normal size uterus; of this group 73 per cent perferred to use radium, 18 per cent x-ray, and 9 per cent either radium or external irradiation. Of the 21 per cent who performed hysterectomy as a method of controlling the bleeding, 33 per cent favored total hysterectomy, none subtotal hysterectomy, and 67 per cent either total or subtotal hysterectomy, depending upon parity or the condition of the cervix.

TABLE I. METHODS OF TREATMENT OF BLEEDING IN THE MENOPAUSAL PERIOD ASSOCIATED WITH SMALL MYOMAS AND FROM THE NORMAL SIZE UTERUS BY A GROUP OF AMERICAN GYNECOLOGISTS

	IRRADIATION		SURGERY	
Small myomas	57%		43%	
	Radium	62.5%	Total hysterectomy	33%
	X-ray	25.0%	Subtotal hysterectomy	17%
	Either	12.5%	Either	50%
Normal uterus	79%		21%	
	Radium	73%	Total hysterectomy	33%
	X-ray	18%	Subtotal hysterectomy	0%
	Either	9%	Either	67%

For the treatment of small myomas in menopausal patients in whom the only symptom is bleeding, 57 per cent of the group utilize irradiation (62.5 per cent radium, 25 per cent x-ray, and 12.5 per cent either). Surgical removal of the uterus was considered to be the treatment of choice by 43 per cent (17 per cent subtotal hysterectomy, 33 per cent total hysterectomy, and 50 per cent either total or subtotal).

Only 27 per cent of those responding were impressed by either the complications or the mortality associated with irradiation castration. Cervical stenosis followed by retention of secretions within the uterus was mentioned by several as a complication more apt to follow radium insertion than x-ray therapy.

The majority (93 per cent) were of the opinion that the small incidence of carcinoma developing in the irradiated uterus was not sufficient indication for routine hysterectomy.

Summary

While the opinions concerning the best method for treating benign uterine bleeding in a selected group of menopausal patients are divided, the data presented here indicate that irradiation, either by x-ray or radium has certain advantages over surgery.

Even in a group of patients who are good surgical risks for the relatively simple operation of removing a normal sized uterus there will be operative deaths as well as postoperative complications. If irradiation can accomplish the same effect with a much lower morbidity and mortality rate, it might well be utilized more frequently. To achieve the best results from irradiation each case should be considered in the light of indications and contraindications before treatment is instituted and a plan of therapy, designed to produce permanent castration, should be drawn up in advance for each individual. Adequate treatment combined with a careful selection of cases should produce results favorably comparable to those with hysterectomy.

The morbidity associated with the use of either radium or x-ray may be kept at a minimum. A careful evaluation of the history, a thorough pelvic examination and dilatation and curettage to rule out malignancy should precede either x-ray therapy or the insertion of radium. The haphazard use of radium by inexperienced operators may be followed by continuation of the bleeding, complications such as local or generalized sepsis, chronic discharge from radium destruction, cervical stricture, or death of the patient.

The incidence of carcinoma developing in the uterus after irradiation is about 0.6 per cent or the same as that of carcinoma developing in the cervix after subtotal hysterectomy. The number in both groups is even lower when correction is made for those malignancies present when treatment was instituted. Since the deaths from carcinoma developing in the uterus added to the primary mortality associated with x-ray or radium castration must be fewer than the deaths following hysterectomy, it is doubtful that the potential development of carcinoma can be considered as a contraindication to irradiation.

Conclusions

1. Irradiation is a safe effective method of treating benign menopausal bleeding with a mortality rate much lower than for operation.

2. The failures are for the most part due either to poor selection of patients or to inadequate treatment.

3. The only method of eliminating uterine carcinoma is by total extirpation of the pelvic organs. The mortality from this procedure undoubtedly would exceed the combined mortality from irradiation and carcinoma following irradiation.

The author wishes to express his appreciation for the response to the questionnaires from which part of the information used in this paper was compiled.

References

1. Brown, W. E., Kretzschmar, N. R., Peck, W. E., and McGreer, J.: Am. J. Obst. & Gynec. **41**: 295, 1941.
2. Castalow, W. E.: J. A. M. A. **116**: 464, 1941.
3. Corscaden, J. A.: Am. J. Roentgenol. **45**: 661, 1941.
4. Danforth, W. C.: Am. J. Obst. & Gynec. **42**: 587, 1941.
5. Macfarlane, C.: Am. J. Obst. & Gynec. **23**: 108, 1932.
6. Norris, C. C., and Behney, C. A.: Am. Gynec. Soc. Trans. **61**: 197, 1936.
7. Norsworthy, O. L.: Am. J. Roentgenol. **24**: 516, 1933.
8. Pemberton, F.: Am. Gynec. Soc. Trans. **61**: 207, 1936.
9. Weintraub, F.: Am. J. Obst. & Gynec. **36**: 476, 1938.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

A MATERNAL WELFARE PROGRAM FOR NEW ORLEANS

W. F. GUERRIERO, M.D., F.A.C.S., NEW ORLEANS, LA.

(From the Maternal and Child Health Division City Board of Health, and Obstetrical Services, New Orleans Charity Hospital)

IN JULY, 1941, there existed no definite maternal and child health program for the City of New Orleans though there were many scattered facilities which often overlapped and neglected some very vital parts of maternity and child care.

After a period of reorganization, in which the aid of the Charity Hospital (through its Director, Dr. O. P. Daly and its Assistant Clinical Director, Dr. O. Prejean) and the departments of obstetrics and pediatrics Louisiana State University Medical Center and Tulane University was secured, there is now a complete program functioning efficiently. It is this program with some interesting statistics on several new features which is here described.

Antenatal and postnatal care is furnished by Charity Hospital for patients in its vicinity who are to be delivered in that institution. In Algiers and in the St. Bernard Colored Housing Project, both of which are distant from the hospital, clinics for white and colored women are maintained in the former and for colored in the latter. These distant outpatient clinics have relieved some of the excess load of the Charity Hospital clinics and there has been a 60 per cent increase in attendance because of their proximity to the attending patients. In all housing projects of the City there are now established health stations which later will have included antenatal and postnatal clinics as soon as proper medical help may be secured. Patients in these clinics receive their delivery service at Charity Hospital because of the close cooperation between this institution and the Maternal and Child Health Division of the City Health Department.

Two other antenatal and postnatal clinics are maintained for the Louisiana State University Medical Center and Tulane University. These are for colored patients and are located on the south and north sides of the city respectively. In these clinics multiparas under para v and without any complications, are enrolled to serve as home delivery cases for teaching purposes. These cases are delivered in the home by the senior student under the supervision of the respective schools' hospital resident with the assistance of a trained maternity nurse of the Maternal and Child Health Division of the City Health Department. Approximately 60 cases per month are cared for on this service and are used strictly for teaching students the conduct of normal deliveries in the home. All abnormal cases which develop are taken to Charity Hospital. All other home delivery services have been discontinued with the exception of a low cost white service under the supervision of the Child Welfare and Child Health Associations. There are ample hospital facilities maintained by Charity Hospital which obviates the need for home deliveries other than for teaching purposes.

In order to prevent crowding of the hospital services after delivery, it was decided to institute a policy of early discharge of patients who had normal deliveries and provide them with a follow-up home nursing service which had medical advice from the resident staff of Charity Hospital. Much is now being said about

the early discharge of patients after delivery because of war conditions. In the past twelve months, 2926 patients have been sent home between the second and fifth post-partal days and of these only 30 developed complications requiring extra medical care other than nursing care given by the nursing service of Maternal and Child Health Division, which averaged three visits per case. Of these 30, only three were readmitted to the hospital, one for sapremia and two for pyelitis. The remaining 27 exhibited breast complications which were cared for in the home by the nursing staff under the direction of the resident staff. We would like to offer this as evidence that hospital deliveries with early discharge and adequate home follow-up are safer and more economical than home delivery per se. We can visualize this plan being adopted as the solution to present crowded conditions and to the scattered rural populations.

Maternal syphilis has long been present as high as 10 per cent in the colored and in from 2 to 3 per cent in the white patients in New Orleans. At our request, the above previously mentioned authorities of Charity Hospital established obstetrical-maternal syphilis clinics (three for colored, two for white). These clinics use the combined knowledge of the obstetrician and syphilologist to insure the utmost care for these patients. A thorough follow-up and family contact service is provided by the Maternal and Child Health nursing service. After pregnancy has ended, each mother is followed and therapy continued to completely eradicate the infection.

There are approximately 225 cases enrolled in these clinics at the present time and in the past twelve months 370 cases have been treated. With such a program congenital syphilis will be eradicated and eventually the more ideal state of eradication of maternal syphilis will result.

Conclusion

The maternity program of the New Orleans City Health Department has been organized and is now serving the following purposes:

1. To lower maternal and infant mortality and morbidity by giving care, instruction and supervision throughout the maternity cycle to expectant mothers who are unable to pay for a private physician.

2. To relieve congestion in the Charity Hospital maternity clinics and obstetrical wards.

3. To furnish training for physicians, medical students, and nurses.

4. To furnish postnatal care for infants and initiate and stimulate interest in pediatric follow-up examinations.

5. To provide antenatal and postnatal medical and nursing supervision for all expectant mothers who have syphilis or have had syphilis previously. Also, to provide nursing supervision of all family contacts of these mothers.

Acknowledgment is made of the aid of the Committee on Maternal Welfare of the New Orleans Medical Society, and especially to its Chairman, Dr. E. L. Zander.

Department of Statistics

A SURVEY OF CESAREAN SECTIONS IN PHILADELPHIA

Comparison Between Years 1931 and 1941*

CLIFFORD B. LULL, M.D., PHILADELPHIA, PA.

IN 1931 the Council of the Philadelphia Obstetrical Society requested me to make a study of the incidence and mortality of all cesarean sections performed in the city of Philadelphia during that year. The present is a comparative study

TABLE I. INCIDENCE OF CESAREANS AND DEATHS

HOSPITAL	NO. DELIVERIES	NO. SECTIONS	% INCIDENCE	SECTION DEATHS	% DEATHS
1	546	8	1.46	0	0.0
2	733	27	3.68	3	11.1
3	922	80	8.67	0	0.0
4	1001	37	3.69	1	2.7
5	1251	26	2.07	0	0.0
6	215	4	1.86	0	0.0
7	497	14	2.81	1	7.14
8	789	12	1.52	0	0.0
9	1077	26	2.41	1	3.84
10	544	13	2.38	1	7.69
11	818	6	0.73	0	0.0
12	52	17	32.69	0	0.0
13	379	10	2.63	0	0.0
14	673	23	3.41	0	0.0
15	1519	29	1.90	2	6.89
16	2179	122	5.59	1	0.81
17	433	28	6.46	0	0.0
18	172	7	4.06	0	0.0
19	565	8	1.41	1	12.5
20	30	0	0.0	0	0.0
21	547	16	2.92	0	0.0
22	1046	30	2.86	0	0.0
23	1075	25	2.32	0	0.0
24	114	0	0.0	0	0.0
25	728	35	4.80	1	2.85
26	365	13	3.56	0	0.0
27	391	4	1.02	0	0.0
28	505	8	1.58	1	12.5
29	920	10	1.08	0	0.0
30	1376	35	2.54	0	0.0
31	1472	44	2.98	4	9.09
32	1794	80	4.45	2	2.5
33	4	2	50.0	0	0.0
34	1392	8	0.57	0	0.0
35	1169	19	1.62	0	0.0
36	1504	18	1.19	1	5.55
37	136	3	2.20	0	0.0
38	493	20	4.05	1	5.0
39	38	0	0.0	0	0.0
40	277	1	0.36	0	0.0
41	255	9	3.52	1	11.1
42	481	11	2.28	0	0.0
43	141	0	0.0	0	0.0
44	254	5	1.96	0	0.0
45	67	1	1.49	0	0.0
(1941)	30939	894	2.88	22	2.46
(1931)	23511	573	2.43	39	6.80

*Presented at a meeting of the Obstetrical Society of Philadelphia, March 4, 1943.

for the year 1941. There is always some question as to what information may be obtained from these statistical surveys, but I believe that this comparative study will elicit several interesting points. Again we have been able to obtain the whole-hearted cooperation of the hospitals in answering the questionnaire, as well as the assistance of the Division of Vital Statistics of the Department of Public Health and the Maternal Welfare Committee of the County Medical Society. Without their cooperation this presentation would not have been possible.

Table I lists by number the 45 hospitals in Philadelphia practicing obstetrics, the total number of deliveries, the number and incidence of cesarean sections, the number of deaths and the mortality per cent. In this table it will be noted that there was a marked reduction in the mortality rate in 1941 although there was an increase in the incidence of cesarean sections.

Table II shows a comparison between the total number of births and the birth rates in 1931 and 1941, the deliveries occurring in hospitals and the number and percentage incidence of cesarean section. In this table it will be noted that the percentage of hospital deliveries increased from 66.6 in 1931 to 88.4 in 1941 and the incidence of cesarean section increased from 1.6 to 2.5 per cent.

TABLE II. TOTAL INCIDENCE OF CESAREAN SECTION

	1931	1941
Total births in city (live and still)	35,284	34,989
Birth rate per 1,000 population	17.3	17.6
Total births in hospitals	23,511	30,939
Percentage of hospital deliveries	66.6	88.4
Total cesarean sections done	573	894
Per cent of total deliveries	1.6	2.5
Per cent of hospital deliveries	2.4	2.8

Table III shows the parity of patients delivered by the abdominal method in the two surveys.

TABLE III. CESAREANS AND PARITY

	1931	1941
Total cesarean sections	573	894
Primigravidas	284	452
Multigravidas	289	442

Table IV shows the number of patients operated upon before and after the onset of labor, the number that had ruptured membranes, vaginal examinations or attempted vaginal deliveries. In all probability, those patients operated upon when in labor had not progressed further than the very early first stage although the tendency seems to be to give more women a test of labor than heretofore. In 1931 there were five patients upon whom one or more attempts at vaginal delivery were made prior to casarean section and three of them died. In 1941, only three patients fell into this group and none of them died.

TABLE IV. CESAREANS IN RELATION TO LABOR

	1931		1941	
	NO.	%	NO.	%
Number of cesarean sections	573	100.0	894	100.0
Patients in labor	268	46.8	309	34.6
Patients not in labor	305	53.2	585	65.4
Membranes ruptured	108	18.8	136	15.2
Vaginal examinations	156	27.2	137	15.3
Attempted vaginal delivery	5	0.87	3	0.33

Table V shows the indications for operation. As in the previous survey, the term cephalopelvic disproportion includes all the cases of absolute contraction of the pelvis as well as the borderline cases where the fetal head was too large to enter the pelvic inlet. The increased incidence of cesarean section in cases of placenta previa and premature separation of the placenta would lead one to believe that the more radical method of treating these conditions has gained favor in the last 10 years in spite of the fact that there is still quite a controversy as to its advisability. One is impressed with the fact that previous cesarean section as the only indication, increased from 16 to 54. This would also indicate that the dictum "once a cesarean always a cesarean" has gained more followers during the last decade. Another interesting figure is the marked decrease in the number of cases delivered by cesarean section where the only indication was sterilization. This, we believe, might be attributed to the fact that puerperal sterilization done under local anesthesia is more frequently performed than cesarean section with sterilization. As usual, many of the other indications might be questioned. However, it is not the purpose of this paper to criticize but rather to make a plea for standardization of the indications for cesarean operation.

TABLE V. INDICATIONS FOR CESAREAN

	1931	1941
Cephalopelvic disproportion	339	450
Placenta previa	42	79
Toxemia and eclampsia	44	56
Premature separation of placenta	19	55
Previous cesarean as only indication	16	54
Uterine inertia	11	47
Cardiac condition	21	31
Fibroids	0	26
Abnormal presentation	26	20
Tuberculosis	5	7
Recent plastic	5	7
Habitual intrauterine fetal death	0	7
Diabetes Mellitus	0	5
Pelvic tumors	9	4
Elderly primiparas	0	4
Adhesions of old scar	2	4
Kidney disease	0	4
Ruptured uterus	3	3
Elective for sterilization	10	2
Multiple pregnancy	1	2
Appendectomy and appendicitis	0	2
Deformity of hip	2	0
Monstrosity	3	0
Ventral fixation of uterus	3	0
Miscellaneous	12	17
Unknown indication	0	8
Total	573	894

Table VI shows the type of operation performed. In comparison with 1931 when 79.9 per cent cesareans were of the high type, only 61.5 per cent were high cesareans in 1941. There was also a contrast in the proportion of low cesareans done in the two surveys. Obstetricians seem to be accepting the low cesarean operation more generally, particularly in those patients whose membranes have ruptured or who have had vaginal examinations. There were only two extraperitoneal or Waters' modification of the Latsko operation performed. This may be due to the fact that this operation supposedly is more difficult to perform. On the other hand, from my own experience in a rather large obstetric service, I believe it may be due to the fact that fewer patients were permitted to go on indefinitely in labor

and very few had attempts at vaginal delivery before coming to the operating room.

TABLE VI. TYPES OF CESAREAN OPERATION

	1931		1941	
	NO.	%	NO.	%
High	458	79.93	550	61.52
Low	103	17.97	324	36.24
Porro's	10	1.74	17	1.9
Vaginal hysterotomy	1	0.17	0	0.0
Abdominal pregnancy	1	0.17	0	0.0
Extraperitoneal	0	0.0	2	0.22
Not known	0	0.0	1	0.11
Totals	573	100.0	894	100.0

Table VII shows sterilization heading the list of incidental operations. The incidence of hysterectomy instead of myomectomy would lead one to believe that it is the operation of choice where fibromyomata of any size are present in the uterine corpus.

TABLE VII. INCIDENTAL OPERATIONS

	1931	1941
Sterilization	85	212
Hysterectomy	0	25
Salpingo-oophorectomy	5	3
Myomectomy	17	3
Appendectomy	4	1
Lysis of adhesions	0	1
Herniorrhaphy	2	1
Removal of cysts	0	6
Totals	113	252

Table VIII shows the type of anesthesia used. In 1941 inhalation types of anesthesia which included the various gases and ether, were still used more frequently, but it is encouraging to see that there is an increase in the number of cesarean deliveries under local and spinal anesthesia. With the advent of continuous caudal anesthesia, we may in the future expect a very definite decrease in the number of cesareans done under general anesthesia. For a number of years spinal anesthesia was severely condemned in all institutions throughout the city of Philadelphia. However, since the development of fractional spinal anesthesia, there has been a steady increase in its use. During the past year all of the cesarean sections which I personally performed were done under either fractional spinal or continuous caudal anesthesia and the results have been most gratifying.

TABLE VIII. ANESTHESIA USED

	1931		1941	
TYPE	NO.	%	NO.	%
Inhalation	513	89.52	762	85.23
Local	46	8.02	102	11.4
Spinal	14	2.44	28	3.13
Not known	0	0.0	1	0.11
None	0	0.0	1	0.11
Totals	573	100.0	894	100.0

Table IX shows the incidence of live births and stillbirths. It is very encouraging to note the marked decrease in the percentage of still births.

TABLE IX. INCIDENCE OF LIVE AND STILLBIRTHS

	1931		1941	
	NO.	%	NO.	%
Live births	502		874	
Stillbirths	74	12.8	30	3.3
Total births	576		904	

Table X shows the number of cases having had previous cesarean operations. In 1931, 10.2 per cent of the patients with previous cesarean had that as the only indication for the operation, while in 1941 this percentage increased to 21. Practically none of these patients had long labor previous to operation, as shown by the fact that 79 out of 107 were operated upon at the time of election in 1931, and 193 out of 256 in 1941. There was one death in this group in each series.

TABLE X. PREVIOUS SECTIONS

	1931		1941	
	NO.	%	NO.	%
No. having had previous sections	107	100.0	256	100.0
Previous section only indication	11	10.2	54	21.0
Operated at time of election	79	73.8	193	75.4
Operated while in labor	28	26.2	63	24.6
Deaths in this group	1	0.93	1	0.39

Table XI shows the very gratifying decrease in the number of maternal deaths following cesarean section in 1941 as compared with 1931.

TABLE XI. CESAREAN MORTALITY IN ALL HOSPITALS

	1931	1941
No. of cesareans done in all hospitals	573	894
No. of deaths following cesareans	39	22
Percentage of cesarean deaths	6.80	2.46

Table XII shows that although sepsis continues to hold first place as the leading cause of death among the women delivered by cesarean section, it was 9.7 per cent lower in 1941 than in 1931. It is also interesting to note the decrease in the number of deaths listed as hemorrhage and shock. This, in all probability, was due to the prompt and effective use of either plasma or blood which is made possible by the recently established Blood Banks. Attention is also called to the fact that there were no deaths from spinal anesthesia in 1941 in spite of its increased use.

TABLE XII. LEADING CAUSES OF DEATHS FOLLOWING CESAREANS

	1931		1941	
	NO.	%	NO.	%
Sepsis	18	46.15	8	36.36
Hemorrhage and shock	11	28.20	3	13.63
Cardiac conditions	2	5.12	2	9.09
Spinal anesthesia	2	5.12	0	0.0
Nephritic toxemia	1	2.56	1	4.54
Embolism	1	2.56	1	4.54
Others	4	10.25	7	31.81
Totals	39	100.0	22	100.0

Table XIII shows mortality in the various types of cesarean section.

TABLE XIII. MORTALITY IN VARIOUS TYPES OF CESAREAN SECTION

	1931	TOTAL DEATHS		1941	TOTAL DEATHS	
		NO.	%		NO.	%
High	458	31	6.76	550	18	3.27
Low	103	4	3.88	324	4	1.23
Porro	10	4	40.0	17	0	0.0
Extraperitoneal	0	0	0.0	2	0	0.0
Not known	2	0	0.0	1	0	0.0
Totals	573	39	6.8	894	22	2.46

Table XIV shows the indications for cesarean in the fatal cases. This shows a general improvement in all groups.

TABLE XIV. INDICATIONS FOR CESAREAN IN FATAL CASES

	1931	TOTAL DEATHS		1941	TOTAL DEATHS	
		NO.	%		NO.	%
Cephalopelvic disproportion	328	17	5.18	450	10	2.22
Placenta previa	42	3	7.14	79	3	3.79
Toxemia and eclampsia	43	8	18.60	56	4	7.14
Premature separation of placenta	19	3	15.78	55	2	3.63
Uterine inertia	7	1	14.28	47	1	2.12
Cardiac condition	21	2	9.52	31	1	3.22
Tuberculosis	0	0	0.0	7	1	14.28
Brow presentation	6	2	33.33	0	0	0.0
Ruptured uterus	3	2	66.66	0	0	0.0
Cerebrospinal meningitis	1	1	100.0	0	0	0.0
Totals	470	39		725	22	

Summary

A ten year period comparative statistical survey of cesarean sections performed in 45 hospitals throughout the city of Philadelphia is herewith presented. During this period numerous authorities have made a plea for reduction in the incidence of cesarean section, but their efforts have been of no avail as far as the city of Philadelphia is concerned.

The decrease in maternal mortality in spite of the increased number of cesarean sections performed, proves that better judgment has been used in the selection of cases for hospitalization, the time element, the type of operation performed, and the anesthesia used. Errors in judgment where these factors were concerned were probably the most frequent causes of fatalities.

The decrease in maternal and fetal mortality would indicate that cesarean section is now performed when it is truly the procedure of choice and is not used as frequently as a last resort when trial labors and attempted vaginal deliveries have failed.

It has been the consensus of opinion that a statistical survey is of little value, but a comparative statistical survey would seem to be of greater aid in determining whether progress has been made during a definite period of time.

In conclusion, it is recommended that a committee be appointed to make suggestions as to standardization of the various indications for the operation of cesarean section so that in future surveys these indications would be more accurate and less confusing.

Appreciation is expressed to Dr. Ruth Hartley Weaver, Assistant Director of Health of the City of Philadelphia, and Miss Dorothy Malkiel, Secretary of the Maternal Welfare Committee of the County Medical Society, for their assistance in the compilation of these statistics.

Reference

Lull, Clifford B.: Caesarean Section in Philadelphia (A Survey of 1931). Published by the Council of the Philadelphia Obstetrical Society.

807 SPRUCE STREET

Discussion

DR. J. MARCH ALESBURY.—I agree with Dr. Lull that the death rate from cesarean section has decreased. Part of this reduction is due to the use of low cervical section rather than the high in cases contaminated. We must remember that in 1931 we had a total of 269 maternal deaths, of which only 39 deaths followed cesarean section. Accordingly, 14 per cent of the 269 deaths in 1931 were due to cesarean section. In 1941, we had a total of 90 maternal deaths but still had 22 deaths following cesarean, or approximately 24 per cent of the maternal deaths.

In 1941, of the 22 deaths following cesarean, 14 were allocated by the Committee on Maternal Welfare as being P-1 deaths. That means that 63 per cent of the cesarean deaths in 1941 were due to error in judgment, technique, et cetera. When we find that we have an increase in the percentage of maternal deaths from 14 per cent due to cesarean section to 24 per cent, I think we have plenty of room for improvement.

DR. EDWARD SCHUMANN.—I would like to take issue with Dr. Alesbury about the increased percentage of deaths due to cesarean section. The relatively greater number of deaths in cases treated by cesarean section is due to the greater improvement in general obstetrics resulting in an improvement in the maternal death rate as a whole. Unless statistics are broken down you cannot arrive at a sensible conclusion.

If we made a survey of the morbidity and mortality of any surgical operation from 1931 to 1941, you would have comparable improvement in all types of surgery. I expect that if Dr. Lull makes a survey in 1951, he will find a still lower *number* of deaths, but a still higher *percentage* of deaths from cesarean section.

DR. THADDEUS MONTGOMERY.—I would like to ask if the statistics include operative procedures done for rupture of the uterus. I know of two cases of death following such operations and would like to raise the point if it is proper to include the operation "laparotomy" under the head of cesarean section?

The other point to be raised is the question of the extraperitoneal section. A few years ago an enthusiast asked why we had not been doing it and thought we were behind the times, but even at that time, it seemed to me there were very few occasions which called for this operation. If one is to perfect himself in this operation, which is undoubtedly more difficult technically, he has to operate on many patients with the indications practically nonexistent. I doubt that we have the opportunity in the city for one individual to perfect himself in this operation.

DR. NORRIS W. VAUX.—I believe the improvement in mortality is partially due to the fact that the Maternal Welfare Committee in its discussion throughout the City of Philadelphia calls for consultation of obstetricians of reputation after 24 hours of labor without progress, to decide whether or not cesarean section should be performed. I have no reason to suppose that in 1931 these sections were done promiscuously or without consultation, but I am convinced there is something in the improvement of our statistics which the Maternal Mortality Committee has taken cognizance of in urging the hospitals to live up to this consultation program. As has been mentioned, the incidence of deaths is probably higher in the section cases but, after all, the patient is getting better professional treatment, which in the end will show an improvement in maternal death rate from cesarean section. We are improving regardless of weather statistics lie or tell the truth and in 1951 I hope we will see steady improvement and lasting results.

DR. PHILIP F. WILLIAMS.—The Committee on Maternal Welfare used the frequency of types of operation in the first survey in their analysis of cesarean deaths for the first three years' work of the Committee. The present survey shows many points for discussion. One of them is the marked increase in the low cervical section, an advance which has been made very slowly in this city. It is interesting to recall in this connection that Falls of Chicago showed there was not much difference in the mortality between the classical and the low section in a large series of cases. Last year, Schumann's paper made it quite evident that there was not much need for the extraperitoneal type of cesarean section, for at least, one year, 1941, in Philadelphia. For in that year there were very few infected obstructed labors admitted to the hospitals of Philadelphia.

It was interesting to note that one out of four women who had a cesarean section reported in this second survey was sterilized. In twenty-five of these sterilizations the uterus was removed and Dr. Lull has stated that all of these hysterectomies were done because of fibroids. If this is the case, I think we are missing some points to remove the uterus when a hysterotomy has been done in some cases of nephritis or cardiac deaths where we want to sterilize the patient. Stander has made this point clear in his discussion of the treatment of pregnancy and complicating chronic nephritis. I think that if such a high percentage, practically 25 per cent had to be sterilized at the time of cesarean, that the breakdown of the indications of sterilizing them would be of considerable interest.

Finally, I feel that in spite of transfusions and the use of sulfanilamide and the increased use of the low section, that a certain proportion of the reduction in the mortality from cesarean sections shown by comparing the two surveys must be attributed to the open discussions of mortalities in the meetings of our County Medical Society Committee on Maternal Welfare.

DR. LULL (closing).—In going over these records I was distinctly impressed with the improvement which has been shown in the practice of obstetrics during the past decade. Particularly is this improvement evident in those cases upon whom vaginal examinations were performed and whose membranes had ruptured previous to the operation of classical cesarean section. A great deal of credit should be given to the Maternal Mortality Committee for their efforts in bringing about these improvements.

Dr. Montgomery has brought up the question of the Waters' operation. I agree with him that we do not see the badly infected or mishandled case as frequently as we used to and, therefore, the operation is not performed as frequently as in some reported series.

Finally, it has been a great pleasure to see how the question of the type of operation and the anesthetic used, together with adequate fluid balance, blood transfusion, careful preoperative preparation and every sensible postoperative care, have all played an important part in saving the life of a good many patients.

Department of Reviews and Abstracts

Selected Abstracts

Extrauterine Pregnancy

Leech, R. B.: A Case of Combined Intra-Uterine and Extra-Uterine Pregnancy, Brit. M. J. **2**: 805, 1941.

The author reports a case in a Uganda native.

The patient had cyclic bleeding during the first six months of her pregnancy. Two weeks from term, abdominal examination revealed the uterus to be enlarged to a size compatible with menstrual history, but flanked by two masses resembling fetal heads in size. A provisional diagnosis of fibroids was made.

The patient was delivered at term, by the local midwife, following a normal labor, of a five and one-half pound living infant. Two days later, the patient began to complain of abdominal pain, which persisted for three weeks. She then sought aid at the central hospital, where she was delivired by laparotomy of a living six-pound infant which was lying free in the peritoneal cavity. The amniotic sac had ruptured spontaneously, presumably at the time of the onset of symptoms two days following delivery of the intrauterine fetus. The placenta was attached in the region of the right ovary.

Three hundred and six cases of combined pregnancy have been collected by Mitra, of which about 3 per cent resulted in the delivery of both infants alive.

FRED L. ADAIR AND RAYMOND L. YOUNG.

Kulenkampff, D.: Diagnosis of Abdominal Bleeding in Extrauterine Pregnancy, Zentralbl. f. Gynäk. **65**: 379, 1941.

The author discusses the many possibilities of error in attempting to secure abdominal fluid by puncture in suspected hemorrhage of ectopic pregnancy. His criterion for determining that any blood found in the sample drawn by puncture is truly free blood is: rouleaux formation is never seen, but countless erythrocytes have assumed a thorn apple (crenated) shape.

R. J. WEISSMAN.

Ramos, A. P., and Collazo, A. G.: Value of Quantitative Determination of Chorionic Gonadotropin in the Diagnosis of Ectopic Pregnancy, Rev. méd. brasil. **10**: 111, 1941.

From the premise that the production of chorionic gonadotropin is in direct relation to the area affected by placental trophoblastic activity, as evidenced by its quantity in multiple pregnancy, the authors felt that deficiency of implanation areas, which often occur in ectopic pregnancy, would give a relatively low value for chorionic gonadotropin concentration in blood serum. In cases in which there is deficient or subnormal villous implantation in utero, in the first few months of pregnancy values between 1,000 and 1,500 units per liter of blood serum are found. When these values fall below 1,000 units, fetal death is indicated if the content steadily decreases, of very early pregnancy if the values are increasing in serial

tests, soon rising above 1,000 units. In some cases, however, the values are maintained in the neighborhood of 750 units, and when this is added to strongly suggestive physical findings, the diagnosis of ectopic pregnancy is almost certain. Still lower values, yet over a minimum of 150 units suggest ectopic pregnancy with fetal death. Except for tubal abortion of some days' duration, with organization of the hematocele, ectopic pregnancy may be ruled out if chorionic gonadotropin values fall below 150. Over 20 cases are cited in support of the author's work.

R. J. WEISSMAN.

Bretz, M.: Mistaken Diagnosis of Extrauterine Pregnancy due to Prior Perforation of Uterus, Zentralbl. f. Gynäk. **65**: 498, 1941.

A 30-year-old woman whose chief complaint was right lower quadrant pain had aborted six years previously at two months' pregnancy; five years previously she had a normal full-term delivery with onset of severe bleeding seven weeks later. The family physician performed a dilatation and curettage. Since then the patient's menses had been irregular, giving a picture typical of ectopic pregnancy. At laparotomy an enlarged gravid uterus was found. Deeply embedded in the anterior uterine wall was an adhesion as thick as a pencil which passed from the insertion in the uterus to the left between the left tube and ovary, behind the suspensory ligament, crossing the left tube at the uterine cornu, thus more or less strangulating the tube and ovary and passing on across the anterior aspect of the uterus and up to the right colic flexure. The author concludes that an epiploic appendage had been drawn into the uterine perforation by the curette. The affected adnexa were removed and recovery was uneventful.

R. J. WEISSMAN.

Neumann, O.: Infected Interstitial Pregnancy, Zentralbl f. Gynäk. **64**: 1725, 1940.

According to the author's statistics one interstitial pregnancy is found to 100 extrauterine pregnancies. The author discusses the possible fates of the ovum. A para ii, after two months of amenorrhea experienced mild bleeding of four weeks' duration. In the fourth month since the onset of amenorrhea a flow occurred associated with severe cramps. This the patient assumed was her menses. In the middle of the fifth month she was seized with severe lower abdominal pain and was subjected to laparotomy with a diagnosis of ectopic pregnancy with peritonitis. The abdomen was full of purulent exudate redolent of *B. coli*. Streptococci and staphylococci and fusiform bacilli were also found. An egg-sized tumor was found at the right uterine cornu and on its lower aspect a perforation was seen to be exuding pus. Hysterectomy with drainage was done without avail. The uterine wall was 2 cm. thick and a pigeon's egg-sized fetal sac was found in the tumor, with 2 mm. of muscularis on either side. Microscopically diffuse leucocytic infiltration was found in the membranes. The author concludes that the death of the ovum left a necrotic locus minoris resistentiae for invasion by bacteria by hematogenous or other routes. No mention was made as to whether attempts at abortion had been made by the patient.

R. J. WEISSMAN.

Schwarz, M.: Full-Term Ectopic Pregnancy With Viable Infant, Zentralbl f. Gynäc. **65**: 204, 1941.

Schwarz reports a case of extrauterine pregnancy going to full term. The fetus was found enclosed in its amniotic sac and the placenta was implanted on the peritoneal surface of the uterus. There were a few adhesions to the lateral pelvic walls. The child was delivered and breathed spontaneously. The uterus was amputated. Mother and child made an uneventful recovery.

R. J. WEISSMAN.

Pignoli, Renato: Upon the Existence of a Capsular Membrane in Tubal Pregnancy, Ginecologia **18**: Series 2, 443, 1940.

The author reports that he was able to demonstrate the presence of a capsular membrane in each of two cases of tubal pregnancy. This capsular membrane in tubal pregnancy was comparable to the decidua reflexa in intrauterine pregnancy. Two photomicrographs are included in the article.

CLAIR E. FOLSOME.

Ballantyne, E. N., Murray, K., and Fraser, R. J.: Interstitial Pregnancy After Homolateral Salpingectomy, Canad. M. A. J. 43: 560, 1940.

A case of interstitial pregnancy terminating in uterine rupture during the fifth month is reported. The patient had had a previous salpingo-oophorectomy on the same side for an extrauterine pregnancy and a dermoid cyst. At least 25 cases in which an interstitial pregnancy has occurred subsequent to a homolateral salpingectomy are recorded in the literature.

The diagnosis before rupture of the interstitial pregnancy is difficult but should be kept in mind.

The palpation of a mass attached to one cornu by a broad base in the presence of symptoms suggesting pregnancy is characteristic. Cornual excision is the operation of choice in cases where the pregnant sac is not too large and supravaginal hysterectomy in the more advanced cases.

CARL P. HUBER.

Reist, A.: Rare Ectopic Pregnancy in the Form of a Primary Cervical Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. **112**: 65, 1941.

The author reports a case of primary cervical pregnancy and reviews the literature. The mortality among the 44 reported cases was 25 per cent and was chiefly due to hemorrhage. The safest treatment for this rare condition is removal of the uterus as soon as the diagnosis is made. In very early cases, however, it is possible to treat the condition by removal of the pregnancy, ligation of the cervical blood vessels, tamponade, and amputation of the cervix.

J. P. GREENHILL.

Toxemia

Whitacre, Frank E., and Fang, L. Y.: Fatty Degeneration of the Liver in Pregnancy, J. A. M. A. **118**: 1358, 1942.

A case of fatty degeneration of the liver with recovery is reported. A cesarean section was done and the woman recovered. The life of such a patient depends upon vigorous treatment with dextrose and termination of the pregnancy by the most conservative means. Blood chemistry will usually indicate extensive liver damage. The patient had less advanced stage of acute yellow atrophy than is seen usually in pregnancy. It is the belief of the authors that patients with this disease die from hypoglycemia rather than from the extent of the liver damage.

WILLIAM BERMAN.

Foley, E. J.: Toxemia of Pregnancy in the Guinea Pig, J. Exper. Med. **75**: 539, 1942.

A fatal disease of late pregnancy and the early puerperium is reported from the guinea pig colony of the department of Bacteriology of the Notre Dame University. Of the 214 deaths from all causes occurring since July, 1940, 47 seemed to fit this category. The disease was sudden in onset, and marked by prostration

and respiratory distress. Death occurred within twenty-four hours. At autopsy the liver was swollen and bright yellow in color. Microscopically it contained a great deal of fat. There was frequent edema of the lungs and occasional pneumonia. No consistent bacterial agent could be found. The disease occurred in primiparas more often than in multiparas. Unlike the report of Greene of a somewhat similar disease in the rabbit colony of the Rockefeller Institute at Princeton, there were no cases not associated with pregnancy.

T. M. HELLMAN.

Shute, E.: The Use of Vitamin P in the Edema of Pregnancy Toxemia, Canad. M. A. J. **45**: 542, 1941.

A preparation of citrin (vitamin P) was given to 20 edematous women in late pregnancy, with the edema ascribable to pregnancy. It was also given to a pregnant woman in late pregnancy showing cardiac edema and to a nonpregnant woman having hypertension and edema. The visible edema and weight were unaffected in all cases.

CARL P. HUBER.

Lange-Sundermann: Treatment of Hyperemesis Gravidarum With Adrenal Cortex Hormone Cortiron, München. med. Wchnschr. **87**: 808, 1940.

Dr. Lange-Sundermann discusses briefly the physiology of the adrenal cortex in pregnancy and reviews the literature on this subject, and he feels that it has now become quite clear that hormonal hypofunction in pregnancy may be the cause of hyperemesis gravidarum, and that it is necessary in pregnancy to have a hypertrophy of the adrenal in order that the pregnant woman might remain healthy and be able to do her work.

He cites his own series of 27 patients of hyperemesis, placing them in 3 classes according to the severity of their symptoms. He administers a synthetic adrenal cortex hormone (cortiron), his dosage varying with the individual and then gives his results stating that a synthetic adrenal cortex hormone (cortiron) is a very effective, prompt and relatively cheap medication in the treatment of hyperemesis gravidarum.

C. E. PROSHEK.

Demmond, E. Carson: Conservative Treatment of Eclampsia, J. M. A. Georgia **30**: 88, 1941.

In the opinion of the author eclampsia can almost be eliminated by careful prenatal supervision with interruption of the pregnancy before the toxemia is too advanced. Eclamptic convulsions should be controlled by morphine, magnesium sulfate intravenously, and the barbiturates before any measures for delivery are instituted. After recovery from shock, delivery should be consummated by conservative measures, labor being induced by medical means, or artificially rupturing the membrane, with assistance to the patient during the second stage of labor by means of forceps.

Accouchement forcé by manual or instrumental dilatation of the cervix, cervical incisions, or vaginal hysterotomy cannot be too strongly condemned. Cesarean section should not be invoked except in those cases with a strong obstetric indication. Careful postpartum supervision is necessary with particular attention to sedation, blood pressure, and fluid intake and output. Forty ounces of urine a day keeps the convulsions away! No future pregnancies are advisable for at least two or three years, and then only if kidney function, blood pressure, and blood chemistry findings are satisfactory.

J. P. GREENHILL.

Beruti, Josue A., Diradourian, Jorge, and Ahumada, Jorge L.: Results of Treatment for Eclampsia, Arch. de la Clinica Obst. y Ginec. 1: 69, 1942.

This is a statistical study of 339 cases of eclampsia treated in the Obstetrics and Gynecology Clinic "Eliseo Cantón" from 1911 to 1937, with the purpose of comparing radical and conservative methods of treatment. To avoid errors in evaluation the cases were divided into two groups according to the severity of the condition. The indications of the Comite de Londres (1922) were used as criteria. Those cases presenting two of the following five findings were considered severe: (1) coma, (2) pulse above 120, (3) temperature above 39.4 C, (4) systolic blood pressure above 200 mm. and (5) massive albuminuria.

Of the 339 cases, 13.5 per cent occurred ante partum, 64.8 per cent during labor and 21.5 per cent post partum. The total mortality was 18.8 per cent.

The 46 cases of eclampsia during pregnancy (before onset of labor) were divided into four groups according to the treatment employed: (1) active treatment, i.e., abdominal or vaginal cesarean section and all obstetrical manipulations resulting in immediate termination of labor, (2) classical treatment of Stroganoff, i.e., narcotics and sedatives combined in some cases with rupture of membranes and low forceps delivery, (3) the Stroganoff method interrupted or followed by active intervention when the patient's condition remains unimproved or becomes worse, (4) other treatments including venesection, special serums, etc. The authors claim that, despite the small number of cases in each group, the superiority of the Stroganoff method over the active method was definitely shown by the lesser mortality (corrected) in the former (18.1 per cent as compared with 40 per cent). The mortality with the active method was lower when combined with the Stroganoff treatment (22.4 per cent). Treatments other than these two were least effective (mortality 50 per cent). The active method involved a high fetal mortality (40 per cent) which the author feels is not surprising since delivery is almost always by the vaginal route and highly traumatic. With the Stroganoff treatment fetal mortality was only 14.2 per cent. The total fetal mortality in the 46 cases was 25 per cent.

The 220 intra-partum cases of eclampsia were classified according to the treatment as in eclampsias of pregnancy with the addition of a fifth group consisting of active treatment followed immediately by Stroganoff's method in the form advocated by Stoeckel. The mortality with the active method in these cases was 20.3 per cent, less than in the eclampsias of pregnancy. The author believes this is reasonable since labor is less precipitate and operations by the vaginal route are less complicated. When the Stroganoff method was combined with the active method, mortality dropped to 15 per cent. The best results (12.4 per cent mortality) were obtained with the Stroganoff method alone; the worst (47.3 per cent) when the Stroganoff method was abandoned because of the aggravated condition and obstetric intervention (high and low cesarean or "accouchement forcé") was used. The authors consider that this high mortality is in part due to the fact that the cases involved were the most serious ones, but that the change in method also played an important role. The good results in the group given miscellaneous treatments (mortality 13.7 per cent), according to the authors, demonstrates the fallacies which exist in statistics dealing with small numbers. Fetal mortality in the entire series was higher (35.1 per cent) than in the eclampsias of pregnancy and in the group which received Stroganoff treatment followed by active intervention was tremendous (70.5 per cent).

In the 73 cases of puerperal eclampsia the Stroganoff method was not remarkably better than other methods such as venesection and special serums. The authors point out, however, that there were twice as many serious cases in the Stroganoff group as in the group treated by other methods and comparing the two groups according to mortality in these serious cases, the Stroganoff treatment involved half as great a mortality (21.4 per cent as compared to 42.8 per cent).

The data were finally analyzed by dividing the 27 years included in the survey into three periods of nine years each. The total mortality was 21.1 per cent for the first period, decreased to 17.6 per cent in the second and remained at this level (17.1 per cent) in the third period. This lack of progress in the third period is due to an increase in the relative number of serious cases. Fetal mortality was appreciably decreased from 1.05 per cent in the first nine year period to 0.74 per cent in the second and finally 0.31 per cent in the third. The authors attribute this reduction to better prenatal care, better preparation of the doctors and increased education of the public.

The authors conclude that the Stroganoff treatment, in all circumstances, offers the best prospects of survival for both mother and child.

J. P. GREENHILL.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF MARCH 9, 1943

The following papers were presented:

A Twenty-Six Day Human Embryo. Wm. E. Studdiford, M.D. (For original article, see page 230.)

Premature Separation of the Normally Implanted Placenta. John A. O'Regan, M.D. (by invitation). To be published in a later issue.

PHILADELPHIA OBSTETRICAL SOCIETY

MEETING OF FEBRUARY 4, 1943

The following paper was presented:

Fetal Malposition: Prevention and Treatment With Special Reference to Breech Presentations Including Experience at the Johns Hopkins Hospital With 1,400 Cases. Nicholson J. Eastman, M.D. (by invitation).

MEETING OF MARCH 4, 1943

The following papers were presented:

An Unusual Fetal Teratoma, With Interesting Radiologic Aspects. F. F. Borzell, M.D. (by invitation), and L. E. Viteri, M.D. (by invitation).

A Survey of the Cesarean Sections Done in Philadelphia During the Year 1941. Clifford B. Lull, M.D. (For original article, see page 314.)

Clinical and Experimental Studies Suggesting the Probable Role of the Pituitary in the Causation of the Late Toxemia of Pregnancy With Hypertension. J. Q. Griffith, M.D.

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 19, 1943

The following papers were presented:

Excretion of Estrogens and Gonadotropins in Pregnancy. Fred L. Adair, M.D. and Ruth M. Watts, Ph.D. (For original paper, see page 183.)

The Treatment of Syphilis in Pregnancy by the Five-Day Massive Dose Method. Herbert Rattner, M.D. (by invitation). (For original paper, see page 255.)

MEETING OF MARCH 19, 1943

A Panel Discussion on Benign Bleeding at the Time of the Menopause. Radium, Dr. M. E. Davis. **X-ray,** Dr. Herbert E. Schmitz. **Surgery,** N. Sproat Heaney.

MEETING OF APRIL 16, 1943

The following paper was presented:

Carcinoma of the Cervix. Consideration of Certain Factors Pertaining to Its Control. Norman F. Miller, M.D., Ann Arbor, Michigan. (By invitation.)

Item

American Board of Obstetrics and Gynecology

The annual meeting of the Board was held at Pittsburgh, Pennsylvania, from May 20 to May 25, 1943, at which time one hundred and eight candidates were certified.

A number of changes in Board regulations and requirements were put into effect. Several of these changes are designed to broaden the requirements for candidates in Service. Examples are the allowance of a stipulated amount of credit toward special training requirements for men in Service and assigned to general surgical positions, special training allowances on a preceptorship basis for men assigned to obstetric or gynecologic duties in military hospitals and working under the supervision of Diplomates or recognized obstetrician-gynecologists, as well as credit toward the "time in practice" requirement of the Board to be allowed for time in military service.

The Board will no longer require a general rotating internship, but will now accept a one-year intern service, although the rotating internship is preferable. Such services must be in institutions approved by the Council on Medical Education and Hospitals of the A. M. A. Lists of such institutions are published regularly in the Educational Number of *The Journal of the A. M. A.*

The privilege of reopening applications by candidates who have been declared ineligible has been extended to two years from date of filing the application, instead of one year.

The Board has ruled temporarily to excuse men in Military Service from the submission of case records at the stipulated examination times, thereby permitting them to proceed without further delay with the Board examinations. This does not obligate the Board, however, to waive the case record requirement for such candidates. Plans have been made to provide similarly for Service men upon their eventual discharge from the Armed Forces, and to permit the greater use of operations done while in residency or in civilian practice before the War.

The next Part I examination of the Board (written paper and submission of case records) will be held on Saturday afternoon, February 12, 1944, at a place convenient to the location of the candidate, whether he be in civilian or military life. Applications must be in the Office of the Secretary by November 15, 1943, ninety days in advance of the examination date. The time and place of the Spring 1944 (Part II) examination will be announced later.

Prospective applicants or candidates in Military Service are urged to obtain from the Office of the Secretary, a copy of the "Record of Professional Assignments for Prospective Applicants for Certification by Specialty Boards" which will be supplied upon request. This record was compiled by the Advisory Board for Medical Specialties and is approved by the offices of the Surgeons-General, having been recommended to the Services in a circular letter, No. 76, from the War Department Army Service Forces, and referred to as the Medical Officers Service Record. These will enable prospective applicants and candidates to keep an accurate record of work done while in Military Service and should be submitted with the candidate's application, so that the Credentials Committee may have this information available in reviewing the application.

Applications and bulletins of detailed information regarding the Board requirements will be sent upon request to the Secretary's Office, 1015 Highland Building, Pittsburgh, Pennsylvania.

PAUL TITUS, M.D., Secretary.

Candidates certified (total 108) by American Board of Obstetrics and Gynecology at the May, 1943, meeting held at Pittsburgh, Pa.:

Angelucci, Helen M., 1209 S. Broad St., Philadelphia, Pa.
Barber, Richard R., Capt., M.C., 125 Holmes Ave., Glenbrook, Conn.
Barker, John Russell, 1101 Beacon Street, Brookline, Mass.
Belous, Leon P., 1930 Wilshire Blvd., Los Angeles, Calif.
Berman, William, 1st Lt., Station Hospital, Fort Riley, Kan.
Bobrow, Morris L., 590 West End Ave., New York, N. Y.
Borson, Josephine, 2490 Channing Way, Berkeley, Calif.
Bosch, Leon C., 512 Medical Arts Building, Grand Rapids, Mich.
Boyce, Allen C., Capt., Utah Quartermaster Depot, Ogden, Utah
Boyd, Benjamin Hartwell, 56 Fifth Street, N. E., Atlanta, Ga.
Bradbury, William C., 1137 Second St., Santa Monica, Calif.
Brandt, Albert J., 413-17 Dollar Bank Bldg., Youngstown, Ohio
Branscomb, Louise, Woodward Bldg., Birmingham, Ala.
Briscoe, Clarence Conway, Medical Tower, 255 S. 17th St., Philadelphia, Pa.
Bristoll, Donald A., 55 West Main Street, New Britain, Conn.
Brody, Simon, 642 Eastern Parkway, Brooklyn, N. Y.
Burwell, John C., Jr., Capt., Nautilus Hospital, Miami Beach, Fla.
Caffee, Henry Hollis, Clay County, Oneida, Ky.
Cavins, Alexander W., 221 S. 6th St., Terre Haute, Ind.
Chapman, Eugene Rhea, Lt. Col., 11th Reg't. Med. Replacement Training Center, Camp Barkeley, Tex.
Chrisman, Irving, 423 Broadway, Paterson, N. J.
Christie, Frank G. S., 178 George St., Sarina, Ontario
Ciner, Leonard F., Lt., M.C., Post Dispensary Marine Barracks, Quantico, Va.
Conway, James F., 1101 Beacon Street, Brookline, Mass.
Corbit, John D., Jr., 3815 Chestnut St., Philadelphia, Pa.
Cromer, J. Keith, 1801 Eye Street, N. W., Washington, D. C.
Dailey, W. Paul, 901 N. Second St., Harrisburg, Pa.
Daily, William T., 142 Joralemon Street, Brooklyn, N. Y.
Day, Lois A., 102-10 2nd Ave., S. W., Rochester, Minn.
Deeds, D. Dalton, Buffalo General Hospital, Buffalo, N. Y.
Edgerton, Glenn S., Capt., Station Hospital, West Point, N. Y.
Ellis, George J., 1150 Connecticut Ave., N. W., Washington, D. C.
Factor, Joseph Lt., M.C., U.S.N., U. S. Naval Hospital, Philadelphia, Pa.
Fairo, Carroll Judson, Lt. Comdr., U. S. Coast Guard Training Station, St. Augustine, Fla.

Filler, William, 37-18 73rd St., Jackson Heights, N. Y.
Forman, Isador, 2118 Pine Street, Philadelphia, Pa.
Frank, Richard, 25 E. Washington St., Chicago, Ill.
Frankel, Arthur N., Capt., 34th Evacuation Hospital, Camp Barkeley, Tex.
Frankel, Jesse M., Capt., Co. B 5th Bn., M.R.T.C., Camp Pickett, Blackstone, Va.
Galsterer, Edwin C., 128 S. Jefferson Ave., Saginaw, Mich.
Garber, Stanley T., 2500 Melrose Ave., Cincinnati, Ohio.
Gillett, Raymond Earl, Northern Permanente Foundation Hosp., Vancouver, Wash.
Godinez, Marcos A., Lt., M.C., U.S.N., Amphibious Training Base, Camp Bradford, N. O. B., Norfolk, Va.
Goodman, Leroy, Capt., 4738 Oak Street, Kansas City, Mo.
Gordon, Harry, 975 Walton Avenue, New York, N. Y.
Gorman, Arthur J., 122 Commonwealth Avenue, Boston, Mass.
Gulick, James B., 144 So. Harrison St., East Orange, N. J.
Hammerly, Fred, 1105 Equitable Bldg., Los Angeles, Calif.
Hart, Benjamin F., 250 N. Ottawa St., Joliet, Ill.
Hawken, Stafford W., 1150 Connecticut Ave., N. W., Suite 22, Washington, D. C.
Hellman, Louis M., Lt., U.S.N., Johns Hopkins Hospital, Baltimore, Md.
Hill, J. Gibson, 35-63 Eighty-Third St., Jackson Heights, N. Y.
Hinebaugh, Mahlon C., Jr., Medical Tower, 255 S. 17th St., Philadelphia, Pa.
Hochman, Samuel, 325 West 86th St., New York, N. Y.
Hopper, Edward B., 65 South Street, Stamford, Conn.
Huggins, Victor S., 80 Glen Road, Brookline, Mass.
Jones, Charlotte A., 303 East 18th St., New York, N. Y.
Jordan, Frank F., Carnegie Medical Bldg., Carnegie at E. 105th St., Cleveland, Ohio.
Kaderabek, Erwin J., 144 S. Harrison St., East Orange, N. J.
King, Allan E., 1801 Eye Street, N. W., Washington, D. C.
Klor, Samuel J., Capt., 4002 Winthrop Ave., Indianapolis, Ind.
Kraff, Harry, 60 Seaman Avenue, New York, N. Y.
Lambertus, Paul T., Quincy Clinic, Quincy, Ill.
Lampman, Harold Heath, 571 Fisher Bldg., Detroit, Mich.
Lounsbury, James B., 201 N. Front St., Wilmington, N. C.
McLean, Lewis F., 826 W. Delavan Ave., Buffalo, N. Y.
McMann, Walter S. L., Army Air Base, Savannah, Ga.
McMurrey, Allen L., 1204 Eagle St., Houston, Tex.
McSweeney, Daniel J., 47 Bay State Road, Boston, Mass.
Mays, Clifford Raymond, 1753 Line Ave., Shreveport, La.
Mazzola, Nunzio Joseph, 133 Clinton Street, Brooklyn, N. Y.
Melone, Horatio R., 800 Diversey Parkway, Chicago, Ill.
Millen, Robert S., 130 East 67th Street, New York, N. Y.
Miller, Hugh K., Lt., U.S.N.R. Recruiting Division, Headquarters, District of Albany, Room 411, P. O. Bldg., Albany, N. Y.
Moloy, Howard Carman, 875 Park Avenue, New York, N. Y.
Mortimer, Bernard, 104 South Michigan Avenue, Chicago, Ill.
Moss, Abner J., N.Y.P.G. Hosp., 303 E. 20th St. at 2nd Ave., New York, N. Y.
Mullins, Julius H., Major, Station Hospital, Ft. McClellan, Ala.
Murphy, Joseph P., Capt., 79th General Hosp., Camp White, Medford, Ore.
O'Hara, Gerald P., 490 Post Street, San Francisco, Calif.
Patterson, John K., Comdr., 429 E. Padre St., Santa Barbara, Calif.
Pearson, Frederick J., 314 West Fourth Street, Bethlehem, Pa.
Promin, David, 3461 Cottman St., Philadelphia, Pa.
Reid, Duncan E., 319 Longwood Avenue, Boston, Mass.
Reidenberg, Leon, Beth Israel Hospital, Stuyvesant Park, E., New York, N. Y.
Rucker, Edwin Macrae, Station Hospital, Camp Shelby, Miss.
Salmon, Udall J., 875 Fifth Avenue, New York, N. Y.
Sass, Raymond W., 1192 Park Ave. at 94th St., New York, N. Y.
Schantz, Samuel I., 4611—12 Avenue, Brooklyn, N. Y.
Schwegler, Raymond A., Capt., M.C., Station Hospital, Camp Barkeley, Tex.
Seibels, Robert E., 1336 Pickens Street, Columbia, S. C.
Siegal, Henry A., 1st Lt., 310th Medical Battalion, APO 85, c/o Postmaster, Shreveport, La.
Siegel, Irving, Capt., Station Hospital, Randolph Field, Tex.
Silberblatt, W. Beryl, 471 Park Avenue, New York, N. Y.

Sill, Henry W., Henry Ford Hospital, 136 Calvert St., Detroit, Mich.
Soukup, John, 11016 S. Michigan Avenue, Chicago, Ill.
Squire, Jack J., 1100 Park Avenue, New York, N. Y.
Stern, Oscar N., Capt., c/o 184 General Hospital, Fort Devans, Mass.
Stewart, Roger E., Stimson Bldg., Seattle, Wash.
Tatelbaum, Abraham, 176 South Goodman Street, Rochester, N. Y.
Topkins, Paul, Lt., Med., A.U.S., 37th General Hospital, Camp Blanding, Fla.
Walker, Ralph H., 4222 Lankershim Boulevard, North Hollywood, Calif.
Warwick, Harry A., 1034 St. Johns Place, Brooklyn, N. Y.
Weinberg, Arthur, 1462 Greenwood Avenue, Far Rockaway, N. Y.
Weiner, Julius G., 750 Main Street, Hartford, Conn.
Weisman, Abner Irving, 817 West End Avenue, New York, N. Y.
Wilder, Earle M., 2224 Eutaw Place, Baltimore, Md.
Williams, George A., 612 Medical Arts Bldg., 384 Peachtree St., N. E., Atlanta, Ga.

Correspondence

Constriction Rings and Epinephrine

The question of the effect of adrenalin upon constriction rings has been recently revived. In an article in the April issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Brown and Wilder conclude that epinephrine is not only useless in the treatment of this complication but is actually dangerous. They base their conclusions upon some hysterograms (the number was not stated) of the laboring and parturient uterus after the administration of ½ to 1 minim of a 1:1,000 solution intravenously, and upon clinical observations, the nature of which is not stated. The authors take exception to laboratory observations being transferred directly to clinical practice without the necessary critical study to determine their value or safety. Then as an exhibition of their own critical powers, they group under the term "contraction rings" all those variants of uterine contraction known as Bandl's rings, retraction rings, hourglass contractions and others. Further on in the article, it is evident that they include a rigid cervix in the "others." At least they argue that epinephrine does not relax the cervix, for had it done so, the uterine contractions would have expelled the hydrostatic bag. They quote Rudolph to the effect that all are an exaggeration of the normal process of uterine contraction and retraction. From their article one would think that Rudolph made no distinction between the various kinds of rings. As a matter of fact, Rudolph coined the very descriptive term "constriction ring" for the type of ring that formed about the fetus so tightly that no further progress of the birth of the baby was possible so long as the ring persisted. Some of the constriction rings are reversible and some irreversible. Rudolph says the term, retraction ring, should be reserved for the exaggerated line of demarcation between the thickened active part of the uterus and the passive lower uterine segment that forms in an obstructed labor. This ring is not a fixed ring like the constriction ring, but ascends as the lower uterine segment becomes thinner, and unless properly treated, rupture of the uterus may result. If Rudolph's suggestion as to the use of these terms were followed, there would be less confusion.

The authors are equally misleading when they refer to my work. "In 1927 Rucker, working on the hypothesis of the relation of the sympathetic system to uterine contraction, reported a relaxation effect of epinephrine on the contraction rings in dystocia. His records are in part graphic, but for the most part are clinical interpretations." My first communication (*Southern Med. J.* **18**: 412, 1925), which the authors entirely ignored, was entirely "graphic." When I began the investigation, I had no preconceived idea. I was merely trying to find out why in some of my caudal anesthesia cases, there followed cessation of uterine contractions as shown by a recording manometer attached to a Voorhees bag within the cervix, and some were followed by no such effect. When these

records were reviewed "critically," it was seen that when adrenalin was added to the procaine, there was a cessation of uterine contractions. When no adrenalin was added to the procaine solution, the uterine contractions continued unabated. The next step was very simple. The adrenalin was administered hypodermically, independently of any anesthesia and four times out of five there was a cessation of uterine contractions as shown by the kymograph. In 20 per cent of the cases, no effect whatever was observed. This was so contrary to the current opinion of the action of epinephrine that it was a comfort when Bourne and Burn obtained the same results independently in England.

The authors show 6 graphs which were evidently tracings of the originals. These add "color" to their article. They show nothing definite, but one would hardly expect to see any effect from ½ minim of epinephrine. The steeplelike contraction in their second graph could very easily have been a gasp, a sigh, or a cough. There is certainly nothing to show that 5 or 6 minims of epinephrine do not stop uterine contractions.

"It is the authors' impression from clinical observations, that no advantage is obtained from the use of epinephrine in contraction rings. This opinion is based on both abdominal palpation and vaginal examination of patients treated with epinephrine." A constriction ring can be suspected from the character of the "pains" and from the lack of progress, but cannot be diagnosed without introducing the hand into the uterus and feeling it. If you cannot know of the presence of the ring without actually feeling it, how can one judge the effect of adrenalin on this ring by abdominal or vaginal examination. On the other hand, if the patient is anesthetized sufficiently for you to attempt to introduce your hand into the uterus, and you are unable to do so on account of a constriction ring, and without changing the depth of the anesthesia 5 or 6 minims of adrenalin are now given intramuscularly, and in a few minutes you feel the ring disappear and you are able to deliver the baby either by version and extraction or by forceps, you have clinical evidence that epinephrine relaxes the constriction ring. This has happened to me not once but ninety-one times. Twice the ring did not relax.

As to the potential risk of giving epinephrine to a fatigued, dehydrated and shocked patient who is in the excitement phase of ether anesthesia, I have no experience. In the first place I certainly would not give ether to such a patient. In the second place, I would not attempt to make an intrauterine examination when the patient was in the excitement phase of anesthesia. However, there is no evidence that epinephrine would do any harm to such a patient.

M. PIERCE RUCKER, M.D.

Medical Arts Bldg.
Richmond, Va.
June 11, 1943.

Transportation of Semen Specimens

To the Editor:

The customary methods of determining the motility of the male sperm is for the specimen to be collected from the inseminated vagina or from a condom. The fault of the first procedure is that the volume of ejaculate cannot be accurately measured. The wearing of a condom in the axilla to the doctor's office is undesirable.

The suggested method is to permit the condom to slide off and remain in the vagina after intercourse. The neck is knotted and a pad worn to prevent the specimen from dropping out. In this way, the exact amount, consistency and motility can be measured; and the optimum temperature of the vagina will protect the sperm. Of course, the effect of the washed rubber on the viability cannot be avoided.

LEO H. POLLOCK, M.D.

1314 Bryant Bldg.
Kansas City, Mo.
May 20, 1943.